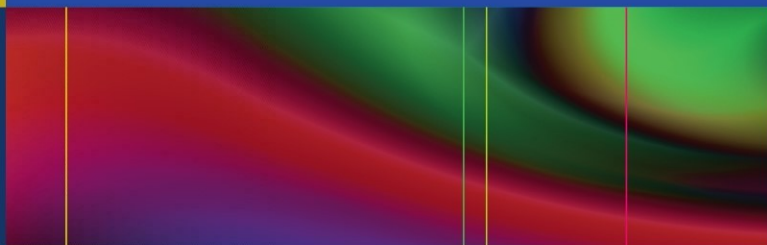


P.N. Patsalos



Antiepileptic Drug Interactions

A Clinical Guide

Second Edition



Springer

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P.N. Patsalos
UCL-Institute of Neurology
Department of Clinical and
Experimental Epilepsy
Queen Square
London

Epilepsy Society
Chalfont Centre for Epilepsy
Chalfont St Peter
UK

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Preface

Since the publication of the first edition of this book in July 2005, much has changed in the field of antiepileptic drug (AED) interactions. Firstly, five new AEDs have been licensed for clinical use (eslicarbazepine acetate, lacosamide, retigabine, rufinamide, and stiripentol); and secondly there has been a surge of publications reporting on interactions involving AEDs, which is reflective of the realization of the importance of drug interaction in clinical therapeutics. In this second edition, a total 27 AEDs are reviewed, in alphabetical order, including AEDs that are not necessarily licensed worldwide but that are prescribed to patients in different countries (e.g., acetazolamide, methsuximide, piracetam, and sulthiame). A noteworthy enhancement in this second edition is the extensive referencing of the various interactions.

AED interactions present a major challenge in the management of epilepsy, and even though our understanding of these interactions has increased substantially, the sheer size of available data has discouraged many physicians from taking an effective approach to minimize the adverse consequences, which may result from these interactions. The purpose of this book is to provide in a systematic fashion a description of the drug interactions that occur between AEDs and between AEDs and non-AED drugs, which may present problems for patients and that often require a drug dose adjustment. With this information, it is anticipated that medical practitioners, who treat patients with epilepsy or patients with morbidities that also require AED use, will be better placed to allow a more rational drug choice when polytherapy regimens are indicated (Patsalos & Bourgeois, 2010).

In addition, the content of this book will allow for a more informed rationale as to how drugs will interact and, therefore, the dosage adjustment that would be consequently necessary to maintain an appropriate therapeutic response (maximal efficacy, minimal adverse effects).

The book is divided into four sections:

The Introduction is a general introduction which explains the basic mechanisms of drug interactions, how to anticipate and predict interactions, and how to prevent and manage adverse interactions.

Part I describes the interactions that occur between AEDs.

Part II describes the interactions that occur between AEDs and non-AED drugs whereby the interaction affects AEDs. The non-AED drugs are listed in drug classes in alphabetical order.

Part III describes the interactions that occur between AEDs and non-AED drugs whereby the interaction affects non-AED drugs. The non-AED drugs are listed in drug classes in alphabetical order.

Because pharmacokinetic interactions represent the majority (>98 %) of described interactions involving AEDs, it is inevitable that the focus of this book is on pharmacokinetic interactions. Nevertheless, pharmacodynamic interactions are equally important and are therefore also described. As a drug class, the number of known interactions involving AEDs is substantial, and while it has been the author's aim to be as complete as possible, the listings may not be exhaustive and the possibility exists that clinically significant interaction will occur with other drugs.

The data used in compiling this book were identified by searches of Medline and PubMed with the terms "antiepileptic drug interactions" combined with individual drug names and drug groups, references from relevant articles, and searches of the author's files. No gender or age limits were imposed but searches, last conducted September 2012, were limited to human subjects. Publications preference in descending

order was as follows: formal interaction studies in patients; formal interaction studies in healthy volunteers; case studies/reports; population pharmacokinetic modeling databases; and therapeutic drug monitoring databases. Papers published in English were preferred but non-English articles were used if they were the sole reference source. Abstracts were included only when a complete published article was not available.

All statements in this book as to the nature of an interaction (pharmacokinetic, pharmacodynamic, or no interaction) are referenced so that the reader can readily identify the appropriate publication. For most such statements, one reference is included (representing the key reference) but where the interaction is controversial two or three references are cited.

The pharmacokinetic interactions presented in this book are described in terms of a change in plasma (blood) levels because physicians treating patients with epilepsy are very familiar with drug plasma levels and how changes in these levels are reflective of a drug's pharmacokinetic characteristics and efficacy/adverse effect profile. However, in some studies, blood levels are not reported and instead clearance, half-life, area under the concentration versus time curve (AUC) and/or maximum blood level (C_{\max}) values are quoted. Thus, for these studies, the interactions are described in terms of changes in clearance, half-life, AUC, and/or C_{\max} values. Whenever available, pharmacokinetic changes in mean values are quoted; otherwise a value representing the most significant change reported, for example in small case series, is quoted. Finally, some studies do not quote any pharmacokinetic variables and instead describe the interaction in terms of a change in the clinical status; for example, patient(s) experienced an enhanced or a reduced therapeutic response or enhanced toxicity. For these interactions, the interactions are described generically, for example "enhances the metabolism" or "inhibits the metabolism" of the affected drug. Wherever the data are available, interactions are also described in relation to their effects on hepatic enzyme

activity; for example, cytochrome P450, uridine glucuronyl transferases, and epoxide hydrolase. This will allow the reader to ascertain the propensity of similar interactions occurring with other drugs that may have similar enzyme activities as substrates, inhibitors and/or inducers. Where pharmacokinetic interactions have been studied but no interaction observed, they are reported as “does not affect the pharmacokinetics of drug...”

When using the information detailed in this book, the reader should remember that although a drug interaction is considered clinically relevant when it results in the need for dosage adjustment or other medical intervention in the majority of patients, a marked deviation in an unusually susceptible individual is also important. Also, one needs to consider the end result because a marked elevation in a low AED/drug level may improve seizure control/therapeutic response while a small elevation of a nearly toxic level may actually precipitate toxicity. Finally, while an interaction involving a 10 % change in a drug blood level may have little, if any, clinical relevance in the majority of patients, it may be of profound clinical relevance in a significant minority of patients.

London

P.N. Patsalos

Disclaimer

The contents of this book are presented in a style so as to alert practitioners as to the potential of an interaction (both pharmacokinetic and pharmacodynamic). The absence of drug listing indicates that the interaction has not been investigated and does not necessary indicate that a drug interaction will not occur. While every effort has been made to summarize accurately and illustrate the published literature, the author does not guarantee the accuracy of the information contained herein. No liability will be assumed for the use of the information contained within this book. Readers should consult any relevant primary literature and the complete prescribing information for each drug.

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Introduction

Epilepsy, which affects approximately 1 % of the world's population, is a chronic disorder that usually persists for many years and often for a lifetime [1]. Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment and complete seizure control can be achieved in the majority (65 %) of newly diagnosed patients by prescribing a single AED, and this is the ideal situation [2]. For the remaining 35 % of patients, the prescribing of polytherapy regimens (the use primarily of two AEDs but often three or four AEDs), so as to achieve optimal seizure control, is a common practice. However, for the majority of these patients little additional benefit is achieved from the use of polytherapy AEDs as intolerable adverse effects commonly occur as a consequence of pharmacokinetic and/or pharmacodynamic interactions. Furthermore, for those patients that respond to monotherapy, they too may experience the consequences of AED interactions as AEDs are added and withdrawn during the optimization of their monotherapy drug regimen [3–5]. A further confounding factor is that since epilepsy is a chronic condition many patients will inevitably develop comorbid diseases or other debilitating conditions and disorders, which will require the co-administration of non-AED drugs. In this setting the potential for drug interactions is considerable [6]. A further source of potential clinically significant interactions that is being increasingly recognized relates to the increasing use of over-the-counter medications and supplements, many of which have unknown constituents and inconsistent quality [7]. Finally, AEDs are increasingly used to treat other non-epilepsy conditions such as mood disorders, migraine,

and pain, thereby further increasing the possibility of combined use with other drugs [8].

The pharmacokinetic properties of AEDs make them particularly susceptible to pharmacokinetic interactions. Furthermore, many AEDs have a narrow therapeutic index in that the plasma (serum) level (concentration) associated with a desirable antiepileptic effect is close to the plasma level that is associated with undesirable adverse effects. Thus, even a relatively small change in their plasma level, consequent to inhibition or induction, may readily result in signs of intoxication or loss of seizure control respectively. In addition, some AEDs exert a major influence on the activity of hepatic drug metabolizing enzymes, stimulating (e.g., carbamazepine, phenytoin, phenobarbital and primidone) or inhibiting (e.g., valproic acid, stiripentol, sulthiame) their activity thereby leading to a wide variety of pharmacokinetic interactions with other drugs that are also metabolized and eliminated by the same enzymes. Conversely, because most AEDs undergo extensive hepatic metabolism (e.g., carbamazepine, eslicarbazepine acetate, lamotrigine, phenytoin, phenobarbital, tiagabine, topiramate, oxcarbazepine, valproic acid, and zonisamide), they too are vulnerable to the effect of other drugs with inhibiting or inducing properties [9].

Mechanisms of Drug Interaction

Drug interactions can be divided into two groups, pharmacodynamic and pharmacokinetic:

1. Pharmacodynamic interactions

Pharmacodynamic interactions occur at the cellular level where drugs act and can occur between drugs that have either similar or opposing pharmacological mechanisms of action. Because these interactions are not associated with any change in plasma drug level, they are less well recognized and documented. Nevertheless, they are of major clinical significance and are invariably concluded by default whereby a change in the clinical status of a patient

consequent to a drug combination cannot be ascribed to a pharmacokinetic interaction.

2. Pharmacokinetic interactions

Pharmacokinetic interactions are characterized by a change in plasma level of either the drug or its metabolite(s) or both. They are particularly prevalent and their magnitude and time course can be readily determined and involve a change in their: absorption, usually gastrointestinal; distribution, usually binding to serum albumin; metabolism, usually by isoenzymes of cytochrome P450 [CYP] and uridine glucuronyl transferases [UGTs]); or elimination, usually renal excretion. Consequently, there is an alteration in the level of the affected drug at the site of drug action.

Pharmacodynamic Interactions

Although pharmacodynamic interactions have been traditionally neglected in epilepsy therapy, increasing evidence indicates that their recognition is essential so as to maximize AED efficacy and minimize AED toxicity. Most pharmacodynamic interactions simply involve additive neurotoxicity, and may be explained by superimposition of adverse events caused by AEDs sharing the same modes of action. For example, combinations of two sodium-channel blockers, such as carbamazepine and oxcarbazepine, or carbamazepine and lamotrigine, are less well tolerated than combinations of drugs acting through different mechanisms. Combinations of drugs that enhance GABAergic inhibition, such as valproic acid and phenobarbital, may result in profound sedation that cannot be explained solely by a pharmacokinetic interaction. Lamotrigine and valproic acid in combination may produce disabling tremor [10]. Examples of potential favorable drug combinations include: valproic acid and ethosuximide in the management of refractory absence seizures [11]; valproic acid and lamotrigine in the management of partial and generalized seizures [12]; and carbamazepine and valproic acid in the management of partial seizures [13].

Pharmacodynamic interactions between AEDs and non-AED drugs can also result in increased toxicity. For example, the concurrent use of lithium and carbamazepine has been associated with a syndrome characterized by somnolence, confusion, disorientation, and ataxia and other cerebella symptoms consequent to a pharmacodynamic interaction [14, 15]. Also, the delirium observed in some patients when quetiapine is co-administered with valproic acid is considered to be the consequence of a pharmacodynamic interaction [16]. Finally, combining carbamazepine with clozapine is generally contraindicated due to concerns about potential additive hematological adverse effects [17].

Pharmacokinetic Interactions

Interactions Affecting Drug Absorption

Interactions affecting the absorption of AEDs are uncommon, although occasionally they do occur and can be important. For example, antacids reduce the absorption of phenytoin, gabapentin, valproic acid, and sulthiame. Furthermore, phenytoin absorption is impaired when the drug is given together with certain nasogastric feeds (e.g., Isocal) so that plasma phenytoin levels are reduced by 72 % [18]. In both examples it is thought that the formation of insoluble complexes may be responsible for the reduced absorption. Other such interactions include a reduction of absorption of primidone by acetazolamide [19] and a reduction in absorption of carbamazepine by colestipol and cisplatin [20, 21].

Plasma Protein Binding Displacement Interactions

Plasma protein-binding displacement interactions are important only with the highly protein-bound (>90 %) AEDs (e.g., phenytoin, tiagabine, valproic acid, and stiripentol). Because these drugs have a low intrinsic hepatic clearance, their

displacement causes an initial transient increase in total drug plasma level prior to re-equilibration and a subsequent decrease. However, the pharmacologically relevant free non-protein bound plasma level is unaffected and thus the clinical effects of the affected AED are unchanged. Consequently, a dosage adjustment is usually unnecessary following displacement of highly protein-bound AEDs from their plasma protein binding sites. A well characterized plasma protein binding displacement interaction is that of phenytoin by valproic acid [22]. However, it is important to recognize that the clinical effects of phenytoin will now correspond to lower total plasma levels and patient management may benefit from monitoring free non-protein bound phenytoin levels [23].

Interactions at the Renal Level

Interactions at the level of renal elimination can be expected to occur with drugs that are predominantly renally eliminated, and indeed such clinically relevant interactions have been described including a decrease in renal clearance and an increase in plasma carbamazepine-10,11-epoxide levels by zonisamide [24] and the decrease in felbamate elimination by gabapentin [25].

Metabolic Interactions

Interactions involving changes in hepatic metabolism represent, by far, most of the pharmacokinetic interactions described with AEDs and involve both induction and inhibition of drug metabolism. Because most AEDs undergo hepatic metabolism they are susceptible to inhibitory and/or induction interactions. These processes are catalyzed by various enzyme systems, which can occur in series, and are referred to as Phase I (functionalization) and Phase II (conjugation) enzyme systems. Phase I reactions include hydroxylation (the addition of a polar functional group) or

N-demethylation (deletion of a non-polar alkyl group) by oxidation, reduction, or hydrolysis. Phase II reactions serve to further increase the water solubility of the drug/metabolite and involve conjugation with glucuronic acid, sulphate, acetate, glutathione, or glycine. Although metabolic drug interactions may involve changes in any one of the numerous enzymes involved in drug metabolism, by far the most important are those associated with the CYP and UGT systems. The CYP system is particularly important because it is not only responsible for the oxidative metabolism of many drugs and exogenous compounds but also of many endogenous compounds such as prostaglandins, fatty acids, and steroids. Metabolic processes serve to convert a drug into one or more metabolites, which are more water-soluble than the parent drug and thus facilitate urinary excretion.

CYP Enzymes

The CYP enzyme system consists of a superfamily of isoenzymes that are located in the smooth endoplasmic reticulum, primarily in the liver but also in many other tissues (e.g., intestine, kidney, brain, and placenta). They are classified into families (the first Arabic number; there is a >40 % amino acid sequence identity within family members), subfamilies (the capital letter that follows; there is a >59 % amino acid sequence identity within subfamily members), and individual isoenzymes (the second Arabic number). Although in man approximately 60 different CYP isoenzymes have been identified, five isoenzymes (CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2C19) are known to be responsible for the metabolism of 95 % of all drugs, and three (CYP2C9, CYP2C19, and CYP3A4) are of particular importance in relation to AED interactions [26]. Because the activity of these isoenzymes is genetically determined, genetic polymorphism resulting in enzyme variants with higher, lower, or no activity, or even resulting in the absence of an isoenzyme can have a profound effect on the pharmacological expression of an interaction (*vide infra*). In relation to AEDs, those

polymorphisms that have clinical consequences relate primarily to CYP2C9 and CYP2C19.

Epoxide Hydrolases

Epoxide hydrolases are a family of enzymes whose function is to convert arene oxides to trans-dihydrodiols and simple epoxides to vicinal diols by hydration and consequently are involved in detoxification processes, although sometimes they are involved in bioactivation reactions [27]. Only the microsomal form of epoxide hydrolase is involved in xenobiotic metabolism and plays an important role in the metabolism of carbamazepine, phenobarbital, and phenytoin. Epoxide intermediates have been implicated in teratogenic events and hypersensitivity reactions and in relation to carbamazepine, carbamazepine-10,11-epoxide is considered to be equipotent to carbamazepine and contributes both to its antiepileptic and adverse effects. Furthermore, epoxide hydrolase inhibition has been implicated in various important interactions involving carbamazepine metabolism (e.g., valproic acid and quetiapine inhibit its activity and increase plasma carbamazepine-10,11-epoxide levels while phenobarbital enhances its activity and decreases plasma carbamazepine-10,11-epoxide levels [28–30]).

Uridine Glucuronyl Transferases

In man, three families of UGTs have been identified, of which UGT1 and UGT2 appear to be the most important in drug metabolism [31]. The UGT1A3 and UGT2B7 isoforms are involved in the O-glucuronidation of valproic acid, while a variety of isoforms (UGT1A6, UGT2B7, UGT2B17, UGT2B4) are involved in the metabolism of eslicarbazepine. UGT1A4 has been found to be the major isoform responsible for the metabolism (N-glucuronidation) of lamotrigine. Although any substrate of UGT has the potential to competitively inhibit the glucuronidation of other substrates by the same

isoform, there are few data in this regard. Furthermore, unlike the CYP system, no specific UGT inhibitors have been identified. Nevertheless, valproic acid inhibits several UGTs while carbamazepine, phenobarbital, and phenytoin are inducers (e.g., interactions with lamotrigine).

Enzyme Inhibition

Enzyme inhibition is the consequence of a competition by drugs to bind to the same enzymic site resulting in a reduction of enzyme activity and a decrease in the rate of metabolism of the affected drug. Inevitably, plasma levels are elevated and this is commonly associated with clinical toxicity. Inhibition is usually competitive in nature and therefore dose-dependent and tends to begin as soon as sufficient levels of the drug inhibitor are achieved, and this usually occurs within 24 h of inhibitor addition. The time to maximal inhibition will depend on the elimination half-life of the affected drug and the inhibiting agent. When the inhibitor is withdrawn, the time course of de-inhibition is dependent on the elimination half-life of the inhibitor. Among the AEDs valproic acid, stiripentol, sulthiame, topiramate, and felbamate have been associated with inhibitory interactions. Furthermore, while topiramate and felbamate are primarily selective inhibitors of CYP2C19, valproic acid is considered to be a broad-spectrum inhibitor of hepatic metabolizing enzymes as it inhibits CYP2C9, UGTs, and microsomal epoxide hydrolase. Stiripentol inhibits CYP2C19 and CYP3A4 while the isoenzymes inhibited by sulthiame are probably CYP2C9 and CYP2C19.

In some circumstances, inhibitory interactions are complicated and problematic. For example, interactions involving the active metabolite(s) of the co-administered drugs may not always be obvious if concurrent plasma level changes of the parent drug do not occur. Because it is not common practice to monitor plasma metabolite levels, if one is unaware of the interaction, blood level monitoring of the parent drug could be misleading. Such problematic interactions are associated with carbamazepine-10,11-epoxide, the pharmacologically

active metabolite of carbamazepine. For example, during carbamazepine combination therapy with either valproate or quetiapine, patients can experience adverse effects as a result of an elevation of carbamazepine-10,11-epoxide levels resulting from an inhibition of epoxide hydrolase, without concurrent changes in plasma carbamazepine levels [28, 30].

An AED may be the affected drug or the cause of an interaction. In fact, with some drug combinations, both the hepatic metabolism of the AED and that of the other drug are altered. For example, during co-medication with ketoconazole and carbamazepine, carbamazepine plasma levels are increased due to inhibition of carbamazepine metabolism [32]. Conversely, the effectiveness of standard dosages of ketoconazole is reduced because carbamazepine enhances the metabolism of ketoconazole [33]. Other bi-directional interactions include those between topiramate and phenytoin, and between valproic acid and lamotrigine.

Several drugs including macrolide antibiotics (e.g., erythromycin and troleandomycin) and hydrazines (e.g., isoniazid) undergo metabolic activation by CYP enzymes so that the formed metabolites bind to the prosthetic hem of CYPs to form stable metabolic intermediates rendering the CYP inactive. As CYP activity can only be restored by synthesis of new enzyme, the effect of such inhibitors may persist well after the elimination of the precursor (parent) drug. This mechanism is involved in the interaction between erythromycin and troleandomycin with carbamazepine (via inhibition of CYP3A4), and between isoniazid and phenytoin (via inhibition of CYP2C9) [34].

Finally, inhibitory interactions can be irreversible in nature in that drugs containing certain functional groups can be oxidized by CYPs to reactive intermediates that subsequently cause irreversible inactivation of the CYP by alteration of hem or protein or a combination of both. An example of these “suicide inhibitors” is the furanocoumarins that are contained in grapefruit juice and irreversibly inhibit CYP3A4. Thus, grapefruit juice inhibits the metabolism of carbamazepine so that mean plasma carbamazepine C_{\max} and AUC values are increased by 40 % [35] (Table 1).

TABLE I Antiepileptic drug effects on hepatic enzymes

Drug	Effect	Enzymes affected
Acetazolamide	None	–
Carbamazepine	Inducer	CYP2C, CYP3A, CYP1A2, EH and UGT
Clobazam	None	–
Clonazepam	None	–
Eslicarbazepine acetate	Inducer (weak)	CYP3A4
	Inducer (moderate)	UGT1A1
	Inhibitor (moderate)	CYP2C9, CYP2C19
Ethosuximide	None	–
Felbamate	Inducer	CYP3A4
	Inhibitor	CYP2C19, β -oxidation
Gabapentin	None	–
Lacosamide	None	–
Lamotrigine	None/weak inducer	UGT
Levetiracetam	None	–
Methsuximide	None	–
Oxcarbazepine	Inducer (weak)	CYP3A4, UGT
Phenobarbital	Inducer	CYP2C, CYP3A, EH, UGT
Phenytoin	Inducer	CYP2C, CYP3A, EH, UGT
Piracetam	None	–
Pregabalin	None	–
Primidone	Inducer	CYP2C, CYP3A, EH, UGT
Retigabine	None	–
Rufinamide	None	–
Stiripentol	Inhibitor	CYP2D6, CYP2C19, CYP3A2

TABLE I (continued)

Drug	Effect	Enzymes affected
Sulthiame	Inhibitor	CYP2C9, CYP2C19
Tiagabine	None	–
Topiramate	Inducer (weak)	CYP3A4, β -oxidation
	Inhibitor (weak)	CYP2C19
Valproic acid	Inhibitor	CYP2C9, EH, UGT
Vigabatrin	None	–
Zonisamide	Inhibitor	CYP2C9, CYP2C19, CYP2A6, CYP2E1

The above data are based on both in vitro and in vivo data
CYP cytochrome P450, *EH* epoxide hydrolase (microsomal), *UGT*
 uridine glucuronyl transferases

Enzyme Induction

Enzyme induction is the consequence of an increase in enzyme protein resulting from an increase in gene transcription that is mediated by intracellular receptors. However, enzyme induction may also occur by an inducer-mediated decrease in the rate of enzyme degradation, through stabilization of proteins, as occurs with ethanol induction. Thus, although there are several different mechanisms of enzyme induction, the phenobarbital “type” has been best characterized. Indeed, even though phenobarbital is the prototype enzyme-inducing drug, many other drugs (e.g., carbamazepine, phenytoin, primidone, and rifampicin) also enhance drug metabolizing enzymes with induction patterns that overlap that of phenobarbital. The enzymes associated with phenobarbital “type” induction include CYP1A2, CYP2B6, CYP2C8, CYP3C9, and CYP3A4, epoxide hydrolase, and some UGTs.

Enzyme induction results in an increase in enzyme activity, which in turn results in an increase in the rate of metabolism of the affected drug and therefore leads to a decrease in plasma level and possibly a reduction in the therapeutic response. If the affected drug has a pharmacologically active metabolite, induction can result in increased metabolite

levels and possibly an increase in drug toxicity. The amount of enzyme induction is generally proportional to the dose of the inducing drug. As enzyme induction requires synthesis of new enzymes, the time course of induction (and indeed the reversal of induction upon removal of the inducer) is dependent on the rate of enzyme synthesis and/or degradation and the time to reach plasma steady-state levels of the inducing drug. The latter is usually the rate-limiting step and only occurs at a time which is approximately five elimination half-lives of the inducing drug. Thus, the time course of induction is usually gradual and dose-dependent.

Enzyme induction represents a common problem in the management of epilepsy. Carbamazepine, phenobarbital, phenytoin, and primidone are potent inducers of CYPs, although phenytoin and carbamazepine appear to be less potent inducers at doses used clinically. The elderly appear to be less sensitive than younger adults to inducers and thus there is reduced induction of drug metabolism in the elderly, although the evidence for this is contradictory. The reason for the age-dependent response to inducers is not fully understood. Although enzyme induction generally reduces the pharmacological effect of a drug because of increased drug metabolism, sometimes the formed metabolite has the same pharmacological activity as the parent drug. Thus, the clinical consequence of enzyme induction will be determined by the relative reactivity of the parent drug and the formed pharmacologically active metabolite.

Of the AEDs presently used in clinical practice, carbamazepine, felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, and topiramate at doses of ≥ 200 mg/day are the only drugs that are associated with clinically important hepatic enzyme inducing properties.

Anticipating and Predicting Metabolic Interactions

In the clinical setting, an important objective of the AED treatment is to anticipate and minimize the risks of interactions with other agents. An unexpected loss of seizure control

or development of toxicity during AED therapy often accompanies the addition or removal of a concurrently administered drug.

In the past, drug interactions were identified essentially by serendipity. Typically, patients would complain of adverse effects or an increase in seizure frequency subsequent to the introduction of an additional drug to their drug regimen and upon investigation a drug interaction would be confirmed or refuted. In the late 1980s, formal drug interaction studies became an integral component of AED clinical trial development programs but most drug interaction studies were conducted relatively late in Phase II and Phase III clinical development programs and were based on a strategy that was in turn based on the therapeutic indices of drugs and the likelihood of their concurrent use. More recently, with the availability of human hepatic tissue and recombinant CYP enzymes, *in vitro* systems have been used as screening tools to predict the potential for *in vivo* drug interaction at a much earlier stage of drug development. The use of *in vitro* systems for investigating the ability of a drug to inhibit the metabolism of other drugs provides some of the most useful information in predicting potential drug-drug interactions. Nevertheless, the *in vitro* and clinical evaluation of all drugs with the potential to interact with an AED is not possible prior to licensing and thus interactions continue to come to light subsequent to licensing and during the drugs' availability for general clinical use. Particular sources of such interaction data include case reports, therapeutic drug monitoring databases, and population pharmacokinetic modeling databases [36].

In recent years our understanding of how individual drugs are metabolized has greatly facilitated the prediction of metabolic interactions. While AEDs are metabolized in the liver via numerous pathways such as β -oxidation (e.g., valproic acid) and conjugation involving UGTs (e.g., eslicarbazepine, lamotrigine, oxcarbazepine, retigabine, and valproic acid), by far the most important system for AED metabolism is the CYP system (e.g., clobazam, clonazepam, carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital,

stiripentol, topiramate, tiagabine, and zonisamide). For an accurate prediction of a drug's potential to interact, it is essential to identify the enzyme(s) responsible for the metabolism of the drug. Furthermore, in order to be able to anticipate the possible clinical relevance of an interaction, it is important to determine the relative contribution of the metabolic pathway(s) being inhibited or induced to the overall elimination of the drug. In some cases, a single metabolic reaction may involve multiple isoforms or different enzyme systems, while in other cases all the metabolic reactions of a drug are catalyzed by a single enzyme. The metabolism (S-oxidation) of 10-(*N,N*-dimethylaminoalkyl) phenothiazines is an example of the first scenario in which numerous CYP isoforms, including CYP2A6, CYP2C8, and CYP2D6, are involved in its metabolism. On the other hand the metabolism of indinavir, an HIV protease inhibitor, via four oxidative metabolic reactions (N-oxidation, N-dealkylation, indan hydroxylation, and phenyl hydroxylation), is catalyzed by a single isoform of CYP, namely CYP3A4.

While *in vitro* data can be used to anticipate *in vivo* inhibitory interactions, such data are of very limited value in assessing the enzyme inducing properties of a drug. For AEDs that do not undergo hepatic metabolism (e.g., gabapentin, levetiracetam, pregabalin, and vigabatrin), or those that are metabolized by non-CYP isoenzymes (e.g., lacosamide, rufinamide) and neither inhibit nor induce CYP isoenzymes, these characteristics provide a powerful predictor that these AEDs are unlikely to be associated with pharmacokinetic interactions. Indeed, clinically these AEDs are observed to be non-interacting.

The clinical consequences of enzyme inhibition depend on the plasma level of the inhibitor, its inhibition constant for the enzyme, and the relative contribution of the pathway to the elimination of the affected drug. If the inhibited pathway accounts for only a small fraction (e.g., <30–40 %) of the drug's total clearance, the impact of the interaction on the drug's plasma level and clinical effect will be minimal. Age, genetics, and environmental factors may also influence the

extent of inhibition. The effects of inhibition interactions are usually apparent within 24 h of addition of the inhibitor, with time to the maximal increase in plasma levels determined by the time required for both the inhibitor and affected drug, which will now have a more prolonged half-life, to achieve steady-state. After discontinuation of the inhibitor, the time course for the decrease in plasma levels depends on the same factors.

In contrast to inhibitory interactions, interactions involving induction can be substantial even if induction involves a minor pathway of drug elimination. In this setting, the minor pathway may become the major pathway responsible for drug clearance causing a clinically relevant decrease in plasma levels.

Interactions with phenytoin, whereby the hepatic enzyme primarily responsible for the metabolism of phenytoin is the isoenzyme CYP2C9 (>80 %) while CYP2C19 contributes <20 % to the metabolism of phenytoin, need more thoughtful consideration. Thus, if amiodarone, fluconazole, miconazole, ketoconazole, propoxyphene, or valproic acid (which inhibit CYP2C9) are co-administered with phenytoin, they will have a substantial potential to inhibit phenytoin metabolism and elevate plasma phenytoin levels. In contrast, if topiramate, cimetidine, felbamate, omeprazole, fluoxetine, or ticlopidine (which inhibit CYP2C19) are co-administered with phenytoin they will only have a small potential to inhibit phenytoin metabolism and elevate plasma phenytoin levels. However, while CYP2C19 is a minor pathway for phenytoin metabolism, its relative contribution increases at higher plasma phenytoin levels due to saturation of the primary phenytoin pathway, CYP2C9. Thus, interactions with CYP2C19 inhibitors, while of minor importance at low phenytoin plasma levels, assume greater significance as plasma phenytoin levels increase. Consequently, patients with phenytoin plasma levels above the saturable level for CYP2C9, which occur at or below the therapeutic range, are more prone to significant elevations in phenytoin plasma levels with the addition of CYP2C19 inhibitors.

Many interactions are associated with large inter-subject variability. In the case of interactions involving phenytoin, this can be explained by various factors. Firstly, there is significant inter-subject variability in the contribution of CYP2C9 and CYP2C19 to its metabolism. Secondly, it is known that drugs that inhibit CYP2C19 (without inhibiting CYP2C9), including carbamazepine, omeprazole, ticlopidine, felbamate, and topiramate, produce inconsistent elevations in phenytoin plasma levels. Thirdly, there is pharmacogenetic variability in CYP expression and a significant proportion of Caucasians and Asians exhibit the “poor metaboliser phenotype” of CYP2C19. In such subjects, inhibition of CYP2C19 is not manifested. Lastly, in the case of the interaction with carbamazepine, carbamazepine may increase the clearance of phenytoin through induction of CYP2C9 and/or CYP2C19.

A further confounding factor relates to the fact that drug interactions may relate to specific competitive inhibition of polymorphic enzymes. For example, omeprazole and diazepam are predominantly metabolized by CYP2C19. The CYP2C19 isoform is known to be polymorphic and approximately 2–6 % of Caucasians and 18–22 % of Asians have been found to be poor metabolizers. Thus, patients that are extensive metabolizers of omeprazole, and consequently have a higher baseline metabolism of omeprazole, are more susceptible to enzyme inhibition interactions than are patients that are poor metabolizers of omeprazole. Similarly, extensive metabolizers are more susceptible to enzyme induction than poor metabolizers.

Databases listing substrates, inhibitors, and inducers of different CYP isoenzymes provide an invaluable resource in helping the physician to predict and eventually to avoid potential interactions (Table 2). For example, knowledge that carbamazepine is an inducer of CYP3A4 allows one to predict that it will reduce the plasma level of CYP3A4 substrates such as ethosuximide, tiagabine, steroid oral contraceptives, and cyclosporine. Likewise, the ability of ketoconazole to inhibit CYP3A4 explains the clinically important rise in plasma carbamazepine levels after ingestion of this antifungal agent.

TABLE 2 Metabolic characteristics of antiepileptic drugs and their propensity to affect hepatic metabolism and cause a pharmacokinetic interaction with other AEDs

AED	Hepatic metabolism (%)	Enzymes involved in metabolism	Elimination by renal excretion (%)	Propensity to interact
Carbamazepine	Substantial (98)	CYP1A2, CYP2C8, CYP3A4	Minimal (2)	Substantial
Phenytoin	Substantial (95)	CYP2C9, CYP2C19	Minimal (2)	Substantial
Phenobarbital	Substantial (80)	CYP2E1, CYP2C19	Minimal (20)	Substantial
Primidone	Minimal (35)	CYP2E1, CYP2C9, CYP2C19	Moderate (65)	Substantial
Stiripentol	Substantial (73)	CYP1A2, CYP2C19, CYP3A4	Minimal (27)	Substantial
Sulthiame	Moderate (68)	Not identified but involve CYP isoenzymes	Minimal (32)	Substantial
Valproic acid	Substantial (97)	CYP2A6, CYP2C9, CYP2C19, CYP2B6, UGT1A3, UGT2B7	Minimal (3)	Substantial
Lamotrigine	Substantial (90)	UGT1A4, UGT1A1, UGT2B7	Minimal (10)	Moderate
Clobazam	Substantial (100)	CYP3A4	None (0)	Minimal
Clonazepam	Substantial (99)	CYP3A4	Minimal (1)	Minimal

(continued)

TABLE 2 (continued)

AED	Hepatic metabolism (%)	Enzymes involved in metabolism	Elimination by renal excretion (%)	Propensity to interact
Elis carbazepine acetate	Substantial (>99)	Not identified but UGTs are involved	Minimal (1)	Minimal
Ethosuximide	Substantial (80)	CYP2B, CYP2E1, CYP3A4	Minimal (20)	Minimal
Felbamate	Moderate (50)	CYP3A4, CYP2E1	Moderate (50)	Minimal
Methsuximide	Substantial (99)	CYP2C19	Minimal (1)	Minimal
Ox carbazepine	Substantial (>99)	Not identified but UGTs are involved	Minimal (<1)	Minimal
Retigabine	Moderate (50–65)	UGT1A1, UGT1A3, UGT1A4, UGT1A9	Minimal (20–30)	Minimal
Rufinamide	Substantial (96)	Unknown (but not CYP-dependent)	Minimal (4)	Minimal
Tiagabine	Substantial (98)	CYP3A4	Minimal (<2)	Minimal
Topiramate	Moderate (50)	Not identified but involve CYP isoenzymes	Moderate (50)	Minimal

Zonisamide	Moderate (65)	CYP3A4	Minimal (35)	Minimal
Acetazolamide	Not metabolized	None	Substantial (100)	Non-interacting
Gabapentin	Not metabolized	None	Substantial (100)	Non-interacting
Lacosamide	Moderate (60)	Demethylation	Minimal (40)	Non-interacting
Levetiracetam	Minimal (30) – non-hepatic, occurs in whole blood	Type-B esterase	Moderate (66)	Non-interacting
Piracetam	Not metabolized	None	Substantial (100)	Non-interacting
Pregabalin	Not metabolized	None	Substantial (98)	Non-interacting
Vigabatrin	Not metabolized	None	Substantial (100)	Non-interacting

Factors That Impact on the Relevance of a Metabolic Interaction

Although the number of theoretically possible interactions based on knowledge of the CYP and other enzyme systems (Table 3) are increasing, it must be appreciated that not all will be of clinical importance. The factors to be considered when evaluating the practical relevance of a potential interaction are as follows:

1. The nature of the interaction at the enzyme site – is it a substrate, an inhibitor, or an inducer?
2. The spectrum of isoenzymes that are induced or inhibited by the interacting agent.
3. The potency of the inhibition/induction – a potent effect will result in a more ubiquitous interaction affecting many/most patients.
4. The concentration (level) of the inhibitor/inducer at the isoenzyme site – drugs that achieve low levels in blood may never reach the level threshold necessary to elicit an interaction.
5. The extent of metabolism of the substrate through the particular isoenzyme – if the affected enzyme is only responsible for a small fraction of the drug's clearance, its inhibition is not going to result in a substantial interaction. Conversely, enzyme induction may increase the activity of the affected enzyme many-fold, and therefore it may increase substantially the total clearance of the drug.
6. The saturability of the isoenzyme – isoenzymes that are saturable at drug levels encountered clinically are more susceptible to significant inhibitory interactions.
7. The route of administration – for drugs showing extensive first-pass metabolism, any change in plasma drug level caused by enzyme induction or inhibition will be much greater after oral than after parenteral administration.
8. The presence of pharmacologically active metabolites – such metabolites complicate the outcome of a potential interaction, and may themselves act as enzyme inducers or inhibitors.

TABLE 3. AED and non-AED drug substrates, inhibitors, and inducers of the major CYP and UGT isoenzymes involved in drug metabolism.

Isoenzymes	Substrates	Inhibitors	Inducers
CYP1A2	AEDs: Carbamazepine, stiripentol Non-AEDs: Aminophylline, amitriptyline, caffeine, clomipramine, chlorpromazine, clozapine, dacarbazine, fluvoxamine, haloperidol, imipramine, lidocaine, melatonin, mirtazapine, olanzapine, paracetamol, phenacetin, propranolol, ropivacaine, sulindac, tacrine, tamoxifen, theophylline, tizanidine, verapamil, <i>R</i> -warfarin, zolpidem, zopiclone	Non-AEDs: Ciprofloxacin Clarithromycin Enoxacin Fluvoxamine Furafylline Methoxsalen Rofecoxib Oral contraceptives	AEDs: Carbamazepine Phenobarbital Phenytoin Primidone Non-AEDs: Rifampicin Ritonavir St. John's wort ^b
CYP2C9	AEDs: Phenobarbital, phenytoin, primidone, valproic acid Non-AEDs: Amitriptyline, celecoxib, diclofenac, dicoumarol, fluoxetine, fluvastatin, ibuprofen, losartan, miconazole, naproxen, olanzapine, phenylbutazone, piroxicam, quetiapine, theophylline, tolbutamide, torasemide, voriconazole, <i>S</i> -warfarin, zidovudine, zolpidem	AEDs: Valproic acid Zonisamide ^a Non-AEDs: Amiodarone Chloramphenicol Delavirdine Efavirenz Fluconazole Fluoxetine Fluvoxamine Miconazole Sulfaphenazole Voriconazole	AEDs: Carbamazepine Phenobarbital Phenytoin Primidone Non-AEDs: Hyperforin Rifampicin Ritonavir St. John's wort

(continued)

TABLE 3 (continued)

Isoenzymes	Substrates	Inhibitors	Inducers
CYP2C19	AEDs: Diazepam, phenobarbital, phenytoin, primidone, stiripentol, valproic acid Non-AEDs: Amitriptyline, citalopram, clomipramine, imipramine, esomeprazole, lansoprazole, moclobemide, omeprazole, pantoprazole, proguanil, propranolol, voriconazole, <i>R</i> -warfarin	AEDs: Eslicarbazepine Felbamate Oxcarbazepine Stiripentol Topiramate ^a Zonisamide ^a Non-AEDs: Cimetidine Delavirdine Efavirenz Esomeprazole Fluconazole Fluvoxamine Lansoprazole Miconazole Omeprazole Ticlopidine Voriconazole	AEDs: Carbamazepine Phenobarbital Phenytoin Primidone Non-AEDs: Rifampicin Ritonavir

CYP2D6

Non-AEDs: Alprenolol, amitriptyline, bufuralol, chlorpromazine, citalopram, clomipramine, clozapine, codeine, debrisoquine, desipramine, dextromethorphan, encainide, flecainide, fluoxetine, fluphenazine, fluvoxamine, haloperidol, imipramine, maprotiline, metoprolol, mianserin, mirtazapine, nefazodone, nortriptyline, olanzapine, paroxetine, perphenazine, phenformin, pindolol, propafenone, propranolol, quetiapine, risperidone, ritonavir, sertindole, tamoxifen, thioridazine, timolol, tramadol, venlafaxine, zuclopenthixol

No inducer known

AEDs:
Stiripentol
Non-AEDs:
Cimetidine
Fluoxetine
Haloperidol
Lansoprazole
Paroxetine
Perphenazine
Propafenone
Quinidine
Terbinafine
Thioridazine
Verapamil

CYP2E1

AEDs: Ethosuximide, felbamate, phenobarbital, primidone
Non-AEDs: Chlorzoxazone, dapsone, ethanol, halothane, isoniazid

Non-AEDs:
Ethanol
Isoniazid

(continued)

TABLE 3 (continued)

Isoenzymes	Substrates	Inhibitors	Inducers
CYP3A4	AEDs: Carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, felbamate, stiripentol, tiagabine, valproic acid, zonisamide Non-AEDs: Alfentanil, amiodarone, amitriptyline, astemizole, atorvastatin, cisapride, citalopram, clarithromycin, clomipramine, clozapine, cyclophosphamide, cyclosporine A, dexamethasone, diltiazem, docetaxel, doxorubicin, erythromycin, etoposide, felodipine, fentanyl, fluoxetine, fluvoxamine, glucocorticoids, haloperidol, ifosfamide, imipramine, indinavir, irinotecan, isoniazid, itraconazole, ketoconazole, lacidipine, lercanidipine, lidocaine, lopinavir, lovastatin, methadone, mirtazapine, nefazodone, nevirapine, nifedipine, nimodipine, olanzapine, oral contraceptives, paclitaxel, procarbazine, proguanil, quetiapine, quinidine, rifampicin, risperidone, ritonavir, saquinavir, sertindole, setraline, sildenafil, simvastatin, steroids, tacrolimus, tamoxifen, teniposide, terfenadine, theophylline, thiotepa, topotecan, trazodone, troleandomycin, venlafaxine, verapamil, vinblastine, vincristine, vindesine, voriconazole, ziprasidone, zolpidem	AEDs: Stripentol Non-AEDs: Amprenavir Cimetidine Clarithromycin Cyclophosphamide Cyclosporine A Delavirdine Dexamethasone Dextropropoxyphene Diltiazem Docetaxel Doxorubicin Efavirenz Erythromycin Etoposide Fluconazole Fluoxetine Fluvoxamine Grapefruit juice Ifosfamide	AEDs: Carbamazepine Escarbazepine Felbamate ^a Oxcarbazepine ^a Phenobarbital Phenytoin Primidone Topiramate ^a Non-AEDs: Cyclophosphamide Dexamethasone Docetaxel Efavirenz Glucocorticoids ^a Nefazodone Nevirapine Paclitaxel Rifabutin Rifampicin St. John's wort Tamoxifen Teniposide

Indinavir
Isontiazid
Itraconazole
Ketoconazole
Lidocaine
Lopinavir
Methadone
Miconazole
Nefazodone
Nelfinavir
Nifedipine
Paclitaxel
Posaconazole
Propoxyphene
Ritonavir
Teniposide
Troleandomycin
Venlafaxine
Verapamil
Vinblastine
Vindesine
Zidovudine

(continued)

TABLE 3 (continued)

Isoenzymes	Substrates	Inhibitors	Inducers
UGT1A4	AEDs: Lamotrigine, eslicarbazepine Non-AEDs: Amitriptyline, clozapine, imipramine, olanzapine	Sertraline Valproic acid	AEDs: Carbamazepine Phenobarbital Phenytoin Primidone Non-AEDs: Oral contraceptives
UGT1A6	AEDs: Valproic acid Non-AEDs: Acetaminophen	Probenecid	AEDs: Carbamazepine Phenobarbital Phenytoin Primidone Non-AEDs: Oral contraceptives
UGT1A9	AEDs: Eslicarbazepine, valproic acid Non-AEDs: Acetaminophen, propofol, tolcapone	Probenecid	AEDs: Carbamazepine Phenobarbital Phenytoin Primidone Non-AEDs: Oral contraceptives

UGT2B7	AEDs: Eslicarbazepine, valproic acid Non-AEDs: Codeine, ibuprofen, morphine, naloxone, naproxen, zidovudine	Atovaquone Fluconazole Probenecid	AEDs: Carbamazepine Phenobarbital Phenytoin Primidone Non-AEDs: Oral contraceptives
UGT2B17	AEDs: Eslicarbazepine		AEDs: Carbamazepine Phenobarbital Phenytoin Primidone
UGT2B4	AEDs: Eslicarbazepine		AEDs: Carbamazepine Phenobarbital Phenytoin Primidone

The list is not exhaustive and is intended for guidance only. Prediction of drug interactions based on this table (see text) are involved in determining whether a clinically significant drug interaction will or will not occur
CYP Cytochrome P450, UGT uridine glucuronyl transferases

^aThese drugs are weak inducers or inhibitors

^bOnly an inducer in females

9. The therapeutic window of the substrate – interactions affecting drugs with a narrow therapeutic window are more likely to be of clinical significance.
10. The plasma level of the affected drug at baseline – any change in plasma drug level will have greater consequences if the baseline level is near the threshold of toxicity (or near the threshold required to produce a desirable therapeutic effect).
11. The genetic predisposition of the individual patient – for example, subjects who show deficiency of a genetically polymorphic isoenzyme (e.g., CYP2D6 or CYP2C19) will not exhibit interactions mediated by induction or inhibition of that isoenzyme.
12. The susceptibility and the sensitivity of the individual in relation to adverse effects – the elderly are more susceptible to interactions because as a patient group they are more likely to receive multiple medications. Also the elderly are more sensitive to the adverse effects of drugs.
13. The probability of the potential interacting drugs being co-prescribed – if a particular combination is unlikely to be co-prescribed, then any potential interaction will be of no clinical relevance.

Prevention and Management of Adverse AED Interactions

From a therapeutic viewpoint, drug interactions are best avoided by use of drugs that are not potent CYP inhibitors or inducers and are not readily inhibited by other drugs. In reality, drug interactions caused by mutual inhibition are almost inevitable, because CYP-mediated metabolism represents a major route of elimination of many drugs and because the same CYP enzymes can metabolize numerous drugs. The clinical significance of a metabolic drug interaction will depend on the magnitude of the change in the concentration of the active species (parent drug and/or metabolites) at the site of pharmacological action and the therapeutic index of

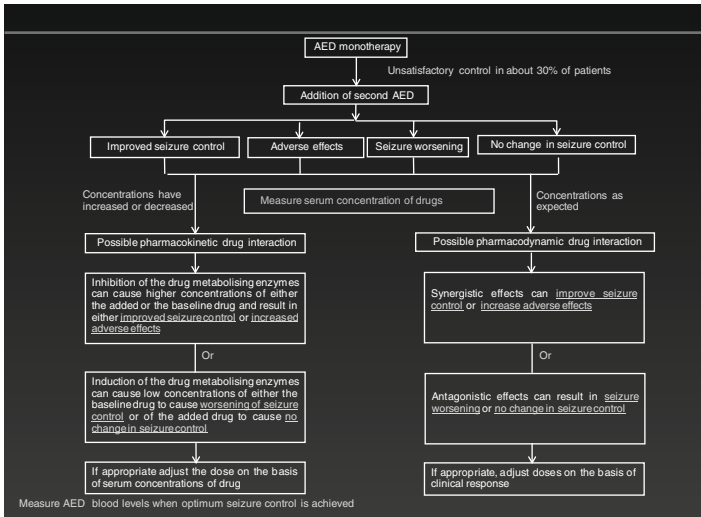


FIGURE 1 Effect of AED interactions on therapeutic outcome (Adapted from Patsalos et al. [3] with permission John Wiley and Sons)

the drug. The smaller the difference between toxicity and efficacy, the greater the likelihood that a drug interaction will have serious clinical consequences.

Prevention of AED interactions is best achieved by avoiding unnecessary polytherapy or by selecting alternative agents that have less potential to interact. The management of interactions begins with anticipating their occurrence and being familiar with the mechanisms involved (Fig. 1). Indeed, awareness of the mechanism of a drug interaction can be used to clinical advantage. For example, when one drug decreases the rate of elimination of another and increases the half-life of the affected drug, this can have an impact on the frequency of dosing, which in turn may improve compliance, or it may mean that a reduction of the dose of the affected drug is necessary. Also, in patients with a sub-therapeutic plasma drug level, elevation of the level may actually result in better seizure control. By following a few simple rules, potential adverse consequences of AED interactions can be minimized or even avoided:

Rule 1

Utilize multiple drug therapy only when it is clearly indicated. Most patients with epilepsy can be best managed with a carefully individualized dosage of a single AED.

Rule 2

If a patient suffers from co-morbidities requiring multiple medications, it is preferable to treat the seizure disorder with an AED having a low interaction potential. Eslicarbazepine acetate, ethosuximide, lamotrigine, topiramate, lacosamide, levetiracetam, retigabine, tiagabine, gabapentin, and pregabalin have little or no ability to cause enzyme induction or inhibition. Among AEDs, the lowest interaction potential is associated with the renally eliminated agents acetazolamide, gabapentin, levetiracetam, piracetam, pregabalin, and vigabatrin.

Rule 3

Be aware of the most important interactions and their underlying mechanisms and any corrective action required (e.g., altered dosing requirements). Most interactions are metabolically based and can be predicted from knowledge of the isoenzymes responsible for the metabolism of the most commonly used drugs and the effects of these drugs on the same isoenzymes.

Rule 4

Avoid combining AEDs with similar adverse effects profiles – for example, benzodiazepines and barbiturates – or drugs associated with additive neurotoxicity, for example, two sodium-channel blockers (carbamazepine and oxcarbazepine, or carbamazepine and lamotrigine). Combining drugs acting through different mechanisms are much better tolerated. Always choose drug combinations for which there is clinical evidence of favorable pharmacodynamic interactions (e.g., ethosuximide and valproate in refractory absence seizures or valproate and lamotrigine in the management of a wide variety of refractory seizures).

Rule 5

Observe clinical response carefully whenever a drug is added or discontinued from the patient's regimen. Consider the

possibility of an interaction if there is an unexpected change in response. Adjust dosage when appropriate.

Rule 6

Be aware that some patient groups (e.g., the elderly, patients with renal or hepatic insufficiency, and during pregnancy) may be more susceptible to interactions and/or more sensitive to the adverse effects of drugs. A contributing confounding factor among these patients is that their pharmacokinetic handling of drugs is altered.

Rule 7

If a pharmacokinetic interaction is anticipated, monitor, if appropriate, the plasma level of the affected drug. Be aware that under certain circumstances (e.g., in the presence of drug displacement from plasma proteins), routine total drug level measurements may be misleading and patient management may benefit from monitoring of free non-protein bound drug levels (e.g., the interaction between valproic acid and phenytoin). In some cases, dosage adjustments may have to be implemented at the time the interacting drug is added or removed. Also, with some drugs, monitoring of surrogate therapeutic markers is preferable over blood level monitoring (e.g., with warfarin and dicoumarol it is advisable to monitor the INR [international normalized ratio] whenever a significant change in therapy of a concomitant enzyme inducing AED is made).

Rule 8

When adding a drug to treat intercurrent or concomitant conditions, choose the one which within a given class is least likely to be involved in worrisome problematic interactions. For example, famotidine would be preferable to cimetidine as an H_2 antagonist, and atenolol would be preferable to metoprolol as a β -adrenoceptor blocker.

Rule 9

Ask patients to report any symptoms or signs suggestive of overdosage or insufficient therapeutic cover.

Rule 10

Inform patients of potential hazards associated with over-the-counter medicines, vitamin supplements, and herbal products.

Many such products are known to interfere with the metabolism of AEDs. Discuss in advance with patients and appropriate alternatives should be suggested, e.g., cold or allergy preparations containing a sympathomimetic amine rather than antihistamines, non-alcoholic formulations of medications, and use of parenteral or oral nonsteroidal anti-inflammatory drugs rather than narcotic analgesics for mild-to-moderate pain control.

The Role of Therapeutic Drug Monitoring in the Management of AED Interactions

Since AED interactions are primarily pharmacokinetic in nature and therefore characterized by a change in drug plasma levels, the role for therapeutic drug monitoring in managing these interactions is very important [23, 37]. For most AEDs there are well-accepted target/therapeutic ranges, however, this is not the case for non-AED drugs. Indeed, for many non-AED drugs there is still debate as to what would be the best parameter for measurement (trough [C_{\min}] or peak [C_{\max}] blood level or the area under the concentration versus time curve [AUC]). The best approach, in most clinical settings, is to undertake a drug level measurement before adding a second drug and then to undertake further drug level measurements and to use the latter values, as necessary, to adjust dosage to achieve the previously effective plasma level and response. It should be remembered, however, that for plasma protein binding displacement interactions, patient management may be best guided by the use of free (non-protein bound) plasma drug levels [23] (Fig. 2).

With some drug interactions, surrogate markers other than plasma drug levels are better suited as a guide to clinical management. For example, it is advisable to monitor the INR (international normalized ratio) with warfarin and dicoumarol whenever a significant change in therapy of a concomitant enzyme inducing AED is made. Also, the determination of the viral load of HIV patients prescribed AEDs and antiviral medication may provide an invaluable indicator of an underlying interaction.

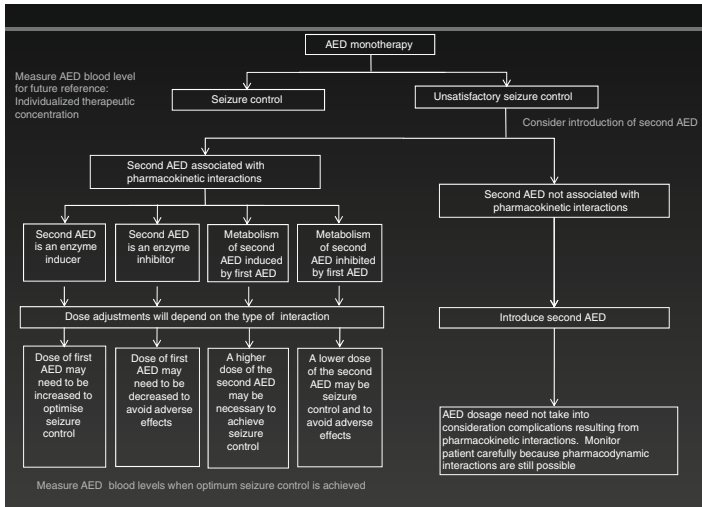


FIGURE 2 Strategies for managing interactions: dosage adjustments based on mechanism of drug interaction (Adapted from Patsalos et al. [3] with permission John Wiley and Sons)

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Part I

Drug Interactions Between AEDs

2 Drug Interactions Between AEDs

TABLE Interactions between antiepileptic drugs (AEDs); expected changes in plasma concentrations (levels) when an AED is added to a preexisting AED regimen

AED added	Preexisting AED									
	<i>CBZ</i>	<i>CLB</i>	<i>CZP</i>	<i>ESL-a</i>	<i>ESM</i>	<i>FBM</i>	<i>GBP</i>	<i>LCM</i>	<i>LTG</i>	<i>LEV</i>
CBZ	AI	CLB↓ DMCLB↑	CZP↓	ESL↓	ESM↓	FBM↓	↔	↔	LTG↓	LEV↓
CLB	CBZ↑ CBZ-E↑	—	NA	↔	?	NA	NA	NA	↔	↔
CZP	↔	NA	—	NA	NA	↔	NA	NA	↔	↔
ESL-a	↔	↔	NA	—	NA	NA	↔	NA	LTG↓	↔
ESM	↔	NA	NA	NA	—	NA	NA	NA	↔	↔
FBM	CBZ↓ CBZ-E↑	CLB↓ DMCLB↑	CZP↑	?	?	—	NA	NA	LTG↑	↔
GBP	↔	NA	NA	↔	NA	FBM↑	—	NA	↔	↔
LCM	↔	NA	↔	NA	NA	NA	↔	—	↔	↔
LTG	↔	↔	CZP↓	↔	↔	↔	NA	↔	—	LEV↓
LEV	↔	↔	↔	↔	↔	NA	↔	↔	↔	—
OXC	CBZ↓	?	?	NCCP	?	?	NA	NA	LTG↓	LEV↓
PB	CBZ↓	CLB↓ DMCLB↑	CZP↓	?	ESM↓	↔	↔	LCM↓	LTG↓	LEV↓
PHT	CBZ↓	CLB↓ DMCLB↑	CZP↓	ESL↓	ESM↓	FBM↓	↔	LCM↓	LTG↓	LEV↓
PGB	↔	NA	NA	NA	NA	NA	↔	NA	↔	↔
PRM	CBZ↓	?	CZP↓	?	ESM↓	?	NA	?	LTG↓	↔
RTG	↔	NA	NA	?	NA	NA	NA	NA	LTG↓	NA
RFN	CBZ↓	↔	NA	NA	NA	NA	NA	NA	LTG↓	NA
STP	CBZ↑	CLB↑ DMCLB↑	?	?	ESM↑	?	NA	NA	?	NA
TGB	↔	NA	NA	NA	NA	NA	NA	NA	↔	↔
TPM	↔	?	?	ESL↓	NA	?	NA	↔	↔	↔
VPA	CBZ-E↑	↔	?	↔	ESM↑↓	FBM↑	↔	↔	LTG↑	↔
VGB	CBZ↑↓	NA	NA	NA	NA	↔	NA	NA	↔	↔
ZNS	CBZ-E↑	?	?	NA	?	?	NA	NA	↔	NA

CBZ carbamazepine, *CBZ-E* carbamazepine-10,11-epoxide (active metabolite of *CBZ*), *CLB* clobazam, *CZP* clonazepam, *DMCLB* N-desmethylclobazam (active metabolite of *CLB*), *ESL-a* eslicarbazepine acetate, *ESL* eslicarbazepine (active metabolite of *ESL-a*), *ESM* ethosuximide, *FBM* felbamate, *GBP* gabapentin, *H-OXC* 10-hydroxy-oxcarbazepine (active metabolite of *OXC*), *LCM* lacosamide, *LEV* levetiracetam, *LTG* lamotrigine, *OXC* oxcarbazepine, *PB* phenobarbital, *PHT* phenytoin, *PGB* pregabalin, *PRM* primidone, *RET* retigabine, *RFN* rufinamide, *STP* stiripentol,

<i>OXC</i>	<i>PB</i>	<i>PHT</i>	<i>PGB</i>	<i>PRM</i>	<i>RTG</i>	<i>RFN</i>	<i>STP</i>	<i>TGB</i>	<i>TPM</i>	<i>VPA</i>	<i>VGB</i>	<i>ZNS</i>
H-OXC↓ ↔		PHT↑↓ ↔		PRM↓	RTG↓	RFN↓	STP↓	TGB↓	TPM↓	VPA↓ ↔		ZNS↓
				PB↑ ?								
↔	↔	PHT↑	NA	PRM↑	NA	↔	STP↑ ?	?		VPA↑	NA	NA
NA	↔	PHT↑↓	NA	↔	NA	NA	NA	?	NA	↔	NA	↔
NCCP	↔	PHT↑	NA	NA	?	NA	NA	NA	TPM↓	VPA↓	NA	NA
NA	↔	↔	NA	PRM↑	NA	NA	NA	NA	NA	VPA↓	NA	NA
↔	PB↑	PHT↑	NA	?	?	?	?	?	?	VPA↑	VGB↓	?
NA	↔	↔	PGB↓	NA	NA	↔	NA	NA	↔	↔	NA	NA
H-OXC↓	NA	↔	NA	NA	NA	NA	NA	NA	↔	↔	NA	↔
↔	↔	↔	↔	↔	RTG↑	↔	NA	NA	↔	VPA↓	NA	↔
NA	↔	↔	↔	↔	NA	NA	NA	NA	↔	↔	↔	NA
—	PB↑	PHT↑	NA	?	?	RFN↓	?	?	TPM↓	↔	NA	NA
H-OXC↓	AI	PHT↑↓ ↔		NCCP	RTG↑	RFN↓	STP↓	TGB↓	TPM↓	VPA↓ ↔		ZNS↓
H-OXC↓	PB↑	AI	PGB↓	PRM↓	RTG↓	RFN↓	STP↓	TGB↓	TPM↓	VPA↓ ↔		ZNS↓
				PB↑								
NA	↔	↔	—	NA	NA	NA	NA	TGB↓	↔	↔	NA	NA
?	NCCP	↔	NA	—	?	RFN↓	STP↓	TGB↓	TPM↓	VPA↓ ↔		ZNS↓
?	PB↑	↔	NA	NA	—	NA	NA	NA	↔	↔	NA	NA
NA	PB↑	PHT↑	NA	NA	NA	—	NA	NA	↔	↔	NA	NA
?	PB↑	PHT↑	NA	PRM↑	?	?	—	?	?	VPA↑	NA	?
NA	NA	↔	NA	NA	NA	NA	NA	—	NA	VPA↓	NA	NA
↔	↔	PHT↑	↔	↔	↔	↔	NA	?	—	VPA↓	NA	NA
↔	PB↑	PHT↓*	↔	PB↑	↔	RFN↑	↔	↔	TPM↓	—	↔	↔
NA	↔	PHT↓	NA	↔	NA	RFN↓	NA	NA	NA	↔	—	NA
?	↔	↔	NA	↔	?	?	?	NA	NA	↔	NA	—

TGB tiagabine, *TPM* topiramate, *VPA* valproic acid, *VGB* vigabatrin, *ZNS* zonisamide

AI autoinduction, *NA* none anticipated, *NCCP* not commonly co-prescribed, ↔ no change, ↓ a usually minor (or inconsistent) decrease in plasma level, ↓↓ a usually clinically significant decrease in plasma level, ↑ a usually minor (or inconsistent) increase in plasma level, ↑↑ a usually clinically significant increase in plasma level

*Free (pharmacologically active) level may increase; ? = unknown, an interaction could occur

Acetazolamide

Acetazolamide (Fig. 1) corresponds chemically to *N*-(5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl)-acetamide with an empirical formula is $C_4H_6N_4O_3S_2$ and a molecular weight of 222.25.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, acetazolamide is rapidly absorbed ($T_{\max} = 2-4$ h) with a bioavailability of >90 %. Its volume of distribution is 0.3 L/kg, and plasma protein binding is 90–95 %.

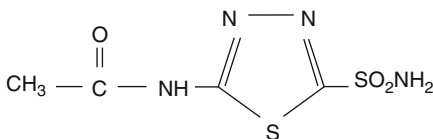


FIGURE 1 Acetazolamide

Biotransformation

Acetazolamide is not metabolized.

Renal Excretion

Approximately 100 % of an administered dose is excreted as unchanged acetazolamide in urine.

Elimination

Plasma elimination half-life values in adults are 10–15 h.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of acetazolamide on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on acetazolamide monotherapy is most likely to occur at plasma acetazolamide levels of 10–14 mg/L (45–63 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ is 4.50 (i.e., 1 mg/L = 4.50 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Acetazolamide affects the pharmacokinetics of other drugs – does not interact.
- Other drugs affect the pharmacokinetics of acetazolamide – does not interact.

Interactions with AEDs

Carbamazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Phenobarbital	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenytoin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated. Sulthiame and acetazolamide are both weak inhibitors of carbonic anhydrase and as a direct result may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Topiramate	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p> <p>Topiramate and acetazolamide are both weak inhibitors of carbonic anhydrase and as a direct result may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur. [1]</p>
Valproic acid	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p>
Vigabatrin	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p>
Zonisamide	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p> <p>Zonisamide and acetazolamide are both weak inhibitors of carbonic anhydrase and as a direct result may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].</p>

Reference

1. Patsalos PN, Bourgeois BFD. The epilepsy prescriber's guide to antiepileptic drugs. Cambridge: Cambridge University Press; 2010.

Carbamazepine

Carbamazepine (Fig. 1) corresponds chemically to 5H-dibenz[b,f]azepine-5-carboxamide with an empirical formula of $C_{15}H_{12}N_2O$ and a molecular weight of 236.27.

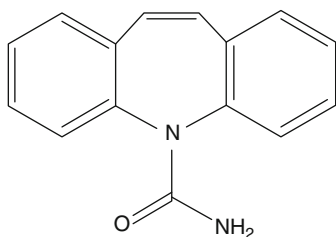


FIGURE 1 Carbamazepine

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, carbamazepine is rapidly absorbed (T_{\max} is formulation-dependent) with a bioavailability of 75–85 %. Its volume of distribution is 0.8–2.0 L/kg, and plasma protein binding is 75 %. The protein binding of the pharmacologically active metabolite, carbamazepine-10,11-epoxide, is 50 %.

Biotransformation

Carbamazepine is extensively metabolized in the liver, primarily by CYP3A4, to carbamazepine-10,11-epoxide which is pharmacologically active. Additional isoenzymes that contribute to the metabolism of carbamazepine include CYP2C8, CYP2B6, CYP2E1, CYP1A2, and CYP2A6. Carbamazepine-10,11-epoxide is in turn metabolized, via epoxide hydrolase, to an inactive trans-carbamazepine diol. Carbamazepine is an enzyme inducer, and additionally, carbamazepine undergoes autoinduction so that its clearance can increase 3-fold within several weeks of starting therapy and this often requires an upward dosage adjustment.

Renal Excretion

Less than 2 % of an administered dose is excreted as unchanged carbamazepine in urine.

Elimination

Following a single dose, plasma elimination half-life values in adults and children are 18–55 h and 3–32 h, respectively. During

maintenance carbamazepine monotherapy, half-life values in adults and children are 8–20 h and 10–13 h, respectively, while in the elderly, carbamazepine half-life values are 30–50 h. The half-life of carbamazepine-10,11-epoxide is ~34 h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Carbamazepine = 2–5 days later
- Carbamazepine-10,11-epoxide = 7 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of carbamazepine on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on carbamazepine monotherapy is most likely to occur at plasma carbamazepine levels of 4–12 mg/L (17–51 $\mu\text{mol/L}$). The upper boundary of the reference range for carbamazepine-10,11-epoxide is 9 $\mu\text{mol/L}$. The conversion factor from mg/L to $\mu\text{mol/L}$ for carbamazepine is 4.23 (i.e., 1 mg/L = 4.23 $\mu\text{mol/L}$) while that of carbamazepine-10,11-epoxide, it is 3.96 (i.e., 1 mg/L = 3.96 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Carbamazepine affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of carbamazepine – substantial.

Interactions with AEDs

Acetazolamide	Affects the pharmacokinetics of carbamazepine.
Consequence	Increases carbamazepine plasma levels via an unknown mechanism [1].
Clobazam	Inhibits the metabolism of carbamazepine.
Consequence	Carbamazepine plasma levels can increase by 15 %, and carbamazepine-10,11-epoxide plasma levels (the pharmacologically active metabolite of carbamazepine) can increase by 87 % [2].
Clonazepam	Does not affect the pharmacokinetics of carbamazepine [3].
Eslicarbazepine acetate	Does not affect the pharmacokinetics of carbamazepine [4]. During combination therapy, carbamazepine enhances eslicarbazepine adverse effects including diplopia, abnormal coordination, and dizziness. These effects are probably the consequence of a pharmacodynamic interaction [5].
Ethosuximide	Does not affect the pharmacokinetics of carbamazepine [6].
Felbamate	Enhances the metabolism of carbamazepine.
Consequence	Mean carbamazepine plasma levels can decrease by 19 %, and mean carbamazepine-10,11-epoxide plasma levels (the pharmacologically active metabolite of carbamazepine) can increase by 33 %. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of carbamazepine-10,11-epoxide via an action on epoxide hydrolase [7].

Gabapentin	Does not affect the pharmacokinetics of carbamazepine [8].
Lacosamide	Does not affect the pharmacokinetics of carbamazepine [9]. Neurotoxicity may occur in combination with carbamazepine, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [10].
Lamotrigine	Does not affect the pharmacokinetics of carbamazepine [11]. The high frequency of neurotoxicity observed with this drug combination represents a pharmacodynamic rather than pharmacokinetic interaction [12].
Levetiracetam	Does not affect the pharmacokinetics of carbamazepine [13]. A pharmacodynamic interaction may occur whereby symptoms of carbamazepine toxicity present [14].
Methsuximide	Enhances the metabolism of carbamazepine.
Consequence	Plasma levels of carbamazepine can decrease by 23 %. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 [15].
Oxcarbazepine	Enhances the metabolism of carbamazepine.
Consequence	Median carbamazepine plasma AUC values can decrease by 9 %, and median carbamazepine-10,11-epoxide plasma AUC values (pharmacologically active metabolite of carbamazepine) can increase by 33 %. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of

	carbamazepine-10,11-epoxide via an action on epoxide hydrolase [16].
Phenobarbital	Enhances the metabolism of carbamazepine.
Consequence	Mean carbamazepine plasma levels can decrease by 33 %, and mean carbamazepine-10, 11-epoxide plasma levels (the pharmacologically active metabolite of carbamazepine) can increase by 24 %. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of carbamazepine-10,11-epoxide via an action on epoxide hydrolase [17].
Phenytoin	Enhances the metabolism of carbamazepine.
Consequence	Mean carbamazepine plasma levels can decrease by 44 %. However, carbamazepine-10, 11-epoxide levels (the pharmacologically active metabolite of carbamazepine) are unaffected. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 [17].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	Does not affect the pharmacokinetics of carbamazepine [18].
Primidone	Enhances the metabolism of carbamazepine.
Consequence	Mean carbamazepine plasma levels can decrease by 25 %, and mean carbamazepine-10,11-epoxide levels (the pharmacologically active metabolite of carbamazepine) can increase by 75 %.

	The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of carbamazepine-10,11-epoxide via an action on epoxide hydrolase [17].
Retigabine	Does not affect the pharmacokinetics of carbamazepine [19].
Rufinamide	Increases the clearance of carbamazepine.
Consequence	The clearance of carbamazepine is increased by 8–15 % so that plasma carbamazepine levels are decreased by 7–13 %. The action is probably the consequence of induction of CYP3A4 [20].
Stiripentol	Inhibits the metabolism of carbamazepine.
Consequence	The clearance of carbamazepine is decreased by 27–70 % so that plasma carbamazepine levels are increased while plasma levels of carbamazepine-10,11-epoxide (the pharmacologically active metabolite carbamazepine) are decreased. The action is the consequence of inhibition, primarily of CYP3A4, but with a minor effect on CYP2C8. Epoxide hydrolase, the enzyme responsible for the metabolism of carbamazepine-10,11-epoxide, is unaffected [21].
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	Does not affect the pharmacokinetics of carbamazepine [22].
Topiramate	Does not affect the pharmacokinetics of carbamazepine [23].

Carbamazepine toxicity has been described in patients co-prescribed with topiramate, and this is considered to be the consequence of a pharmacodynamic interaction [24].

Valproic acid

Inhibits the metabolism of the pharmacologically active metabolite carbamazepine-10,11-epoxide.

Consequence

Mean plasma levels of carbamazepine-10,11-epoxide (the pharmacologically active metabolite carbamazepine), with either no change or a small decrease in plasma carbamazepine levels, can increase by 25 %. This interaction is related to valproic acid inhibition of epoxide hydrolase, the enzyme responsible for the metabolism of the epoxide metabolite [25, 26].

During combination therapy, valproic acid can synergistically enhance the antiepileptic efficacy (partial seizures) of carbamazepine. This effect is the consequence of a pharmacodynamic interaction [27].

Vigabatrin

The effect of vigabatrin on the pharmacokinetics of carbamazepine is controversial.

Consequence

There is a suggestion that in patients with low carbamazepine levels (<9 mg/L), the plasma carbamazepine levels can be significantly increased (20–132 %), through an unknown mechanism, during concomitant administration with vigabatrin. Another study reports that mean carbamazepine levels are decreased by 18 % and that mean carbamazepine clearance increases by 35 % [28, 29].

	During combination therapy, vigabatrin may synergistically enhance the antiepileptic efficacy (partial seizures) of carbamazepine. This effect is probably the consequence of a pharmacodynamic interaction [27].
Zonisamide	Inhibits the metabolism of the pharmacologically active metabolite carbamazepine-10,11-epoxide.
Consequence	Mean plasma carbamazepine-10,11-epoxide C_{\max} and AUC values can increase by 38 and 17 %, respectively. Carbamazepine is not affected. The interaction is the consequence of a decrease in the renal clearance of carbamazepine-10,11-epoxide [30].

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Clobazam

Clobazam (Fig. 1) corresponds chemically to 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione with an empirical formula of $C_{16}H_{13}Cl_2O_2$ and a molecular weight of 300.74.

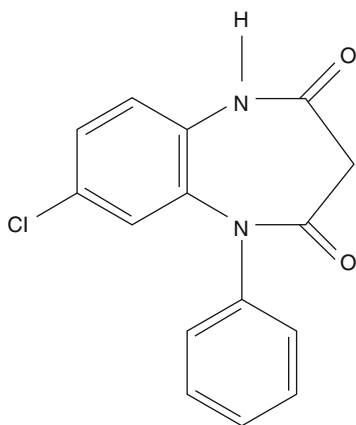


FIGURE 1 Clobazam

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion clobazam is rapidly absorbed ($T_{\max} = 1-3$ h) with a bioavailability of >95 %. Its volume of distribution is 0.87–1.83 L/kg, and plasma protein binding is 85 %. The plasma protein binding of the pharmacologically active metabolite, *N*-desmethyloclobazam, is not known.

Biotransformation

Clobazam is extensively metabolized in the liver, primarily by demethylation, to *N*-desmethyloclobazam, which is pharmacologically active and contributes significantly to the efficacy of clobazam. Clobazam also undergoes metabolism by hydroxylation to form other metabolites, namely, 4-hydroxyclobazam and 4-hydroxy desmethyloclobazam. *N*-desmethyloclobazam is subsequently metabolized by CYP2C19.

Renal Excretion

Less than 1 % of an administered dose is excreted as unchanged clobazam in urine.

Elimination

Plasma elimination half-life values for clobazam and *N*-desmethyloclobazam in adults are 10–30 h and 36–46 h, respectively. In children, clobazam half-life values are ~16 h while in the elderly, clobazam half-life values are 30–48 h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Clobazam = 2–8 days later
- *N*-desmethyloclobazam = 7–10 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of clobazam on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on clobazam monotherapy is most likely to occur at plasma clobazam levels of 0.03–0.30 mg/L (0.1–1.0 $\mu\text{mol/L}$). The reference range for *N*-desmethyloclobazam is 0.30–3.00 mg/L (1–10 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for clobazam is 3.33 (i.e., 1 mg/L = 3.33 $\mu\text{mol/L}$) while that for *N*-desmethyloclobazam it is 3.49 (i.e., 1 mg/L = 3.49 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Clobazam affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of clobazam – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the metabolism of clobazam.
Consequence	Plasma levels of the pharmacologically active metabolite of clobazam, <i>N</i> -desmethyloclobazam, are increased during comedication with carbamazepine. The mean plasma <i>N</i> -desmethyloclobazam/clobazam ratio is increased by 117 % [1].
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Eslicarbazepine acetate	Does not affect the pharmacokinetics of clobazam [2].
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	Inhibits the metabolism of clobazam.
Consequence	Plasma levels of the pharmacologically active metabolite of clobazam, <i>N</i> -desmethyloclobazam, are increased during comedication with felbamate. Typically, the plasma level to weight-adjusted dose ratio of <i>N</i> -desmethyloclobazam can be expected to be 5-fold higher while the ratio for clobazam decreases by 57 %. The interaction may be the consequence of inhibition of <i>N</i> -desmethyloclobazam metabolism through CYP2C19 [3].
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of clobazam [3].
Levetiracetam	Does not affect the pharmacokinetics of clobazam [4].
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital	Enhances the metabolism of clobazam.
Consequence	Plasma levels of the pharmacologically active metabolite of clobazam, <i>N</i> -desmethyloclobazam, are increased during comedication with phenobarbital. The mean plasma

	<i>N</i> -desmethylelobazam/clobazam ratio is increased by 90 % [1].
Phenytoin Consequence	Enhances the metabolism of clobazam. Plasma levels of the pharmacologically active metabolite of clobazam, <i>N</i> -desmethylelobazam, are increased during comedication with phenytoin. The mean plasma <i>N</i> -desmethylelobazam/clobazam ratio is increased by 294 % [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	Does not affect the pharmacokinetics of clobazam [5].
Stiripentol Consequence	Inhibits the metabolism of clobazam. Plasma levels of clobazam and the pharmacologically active metabolite of clobazam, <i>N</i> -desmethylelobazam, are increased during comedication with stiripentol. Typically, the plasma levels of clobazam and <i>N</i> -desmethylelobazam can be expected to be 2-fold higher and 3-fold higher, respectively. The interaction is the consequence of inhibition of <i>N</i> -demethylation of clobazam through CYP3A4 and the inhibition of the hydroxylation of <i>N</i> -desmethylelobazam by CYP2C19 [6].

Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Valproic acid	Does not affect the pharmacokinetics of clobazam [1].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Clonazepam

Clonazepam (Fig. 1) corresponds chemically to 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4 benzodiazepin-2-one with an empirical formula of $C_{15}H_{10}ClN_3O_3$ and a molecular weight of 315.71.

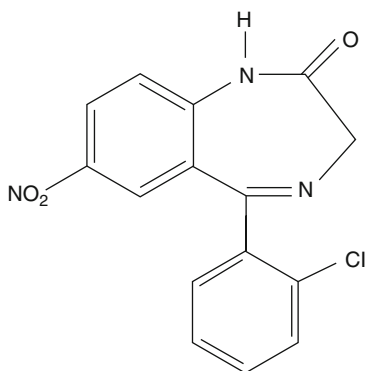


FIGURE 1 Clonazepam

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, clonazepam is rapidly absorbed (T_{\max} = 1–4 h) with a bioavailability of >80 %. Its volume of distribution is 1.5–4.4 L/kg, and plasma protein binding is 86 %.

Biotransformation

Clonazepam is extensively metabolized in the liver by reduction (via CYP3A4) to produce 7-amino-clonazepam which is subsequently metabolized by acetylation (via *N*-acetyltransferase) to form 7-acetamido-clonazepam. Clonazepam is also hydroxylated (isoenzyme not identified) to form 3-hydroxyclozepam. None of the metabolites of clonazepam are pharmacologically active.

Renal Excretion

Less than 1 % of an administered dose is excreted as unchanged clonazepam in urine.

Elimination

In healthy adult subjects, plasma elimination half-life values are 17–56 h while in adult patients with enzyme-inducing antiepileptic drugs, half-life values are 12–46 h. In neonates and children, half-life values are 22–81 h and 22–33 h, respectively.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Adults = 2–10 days later
- Children = 5–7 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of clonazepam on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on clonazepam monotherapy is most likely to occur at plasma clonazepam levels of 13–70 µg/L (41–222 nmol/L). The conversion factor from µg/L to nmol/L is 3.17 (i.e., 1 µg/L = 3.17 nmol/L).

Propensity to Be Associated with Pharmacokinetic Interactions

- Clonazepam affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of clonazepam – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the metabolism of clonazepam.
Consequence	Plasma clonazepam levels can decrease by 19–37 % [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	Inhibits the metabolism of clonazepam.
Consequence	Mean plasma clonazepam levels and AUC values can be increased by 17 and 14 %, respectively [2].
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	Does not affect the pharmacokinetics of clonazepam [3].
Lamotrigine	Enhances the metabolism of clonazepam.
Consequence	Plasma clonazepam levels can decrease by 20–38 % [4].
Levetiracetam	Does not affect the pharmacokinetics of clonazepam [5].
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital	Enhances the metabolism of clonazepam.
Consequence	Mean plasma clonazepam clearance is increased by 19–24 %, and mean plasma clonazepam levels can decrease by 11 % [6].
Phenytoin	Enhances the metabolism of clonazepam.
Consequence	Mean plasma clonazepam clearance can increase by 46–58 %, and mean plasma clonazepam levels can decrease by 28 % [6].

Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	Enhances the metabolism of clonazepam.
Consequence	Plasma clonazepam levels can be decreased [7].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Valproic acid	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Eslicarbazepine Acetate

Eslicarbazepine (Fig. 1) acetate corresponds chemically to (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide with an empirical formula of $C_{17}H_{16}N_2O_3$ and a molecular weight of 296.32.

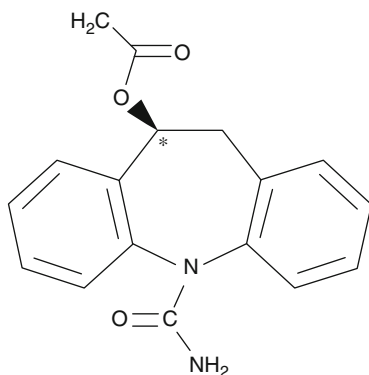


FIGURE 1 Eslicarbazepine

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, eslicarbazepine acetate is rapidly absorbed ($T_{\max}=2-3$ h) with a bioavailability of >90 %. Its volume of distribution is 2.7 L/kg, and plasma protein binding is 30 %. These values relate to eslicarbazepine, the pharmacologically active metabolite of eslicarbazepine acetate.

Biotransformation

Eslicarbazepine acetate is rapidly metabolized (hydrolysis) in the liver to its pharmacologically active metabolite, eslicarbazepine (also known as *S*-licarbazepine and 10-hydroxycarbazepine), by esterases (91 %). Eslicarbazepine (33 %) is subsequently metabolized by conjugation with glucuronic acid. Other minor metabolites, which are pharmacologically active, include *S*-licarbazepine (~5 %) and oxcarbazepine (~1 %). UGT1A4, UGT1A9, UGT2B4, UGT2B7, and (particularly) UGT2B17 are all involved in the conjugation of eslicarbazepine with glucuronic acid.

Renal Excretion

Less than 1 % of an administered dose is excreted as unchanged eslicarbazepine in urine.

Elimination

The plasma elimination half-life of eslicarbazepine acetate is <2 h; thus, eslicarbazepine acetate is a prodrug which is rapidly converted to its eslicarbazepine metabolite. In the absence of enzyme-inducing antiepileptic drugs, half-life values for eslicarbazepine are 10–20 h while in the presence of enzyme-inducing antiepileptic drugs, half-life values are 13–20 h.

Time to new steady-state eslicarbazepine blood levels consequent to an inhibition of metabolism interaction:

- Adults = 2–4 days later

Effects on Isoenzymes

At therapeutic concentrations, eslicarbazepine in vitro is a weak inducer of CYP3A4, a moderate inducer of UGT1A1, and a moderate inhibitor of CYP2C9 and CYP2C19 activities. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and other medicines can be expected.

Eslicarbazepine has no in vitro inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2D, CYP2E1, CYP3A4, and CYP4A9/11; UGT1A1 and UGT1A6; and epoxide hydrolase. Furthermore, eslicarbazepine has no in vitro induction effects on CYP1A2 or CYP3A4.

Therapeutic Drug Monitoring

The current reference range for eslicarbazepine in plasma is 3–35 mg/L (12–139 $\mu\text{mol/L}$) which is based on that for racemic 10-hydroxycarbazepine derived from oxcarbazepine. The conversion factor from mg/L to $\mu\text{mol/L}$ for eslicarbazepine is 3.96 (i.e., 1 mg/L = 3.96 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Eslicarbazepine acetate affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of eslicarbazepine acetate – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the clearance of eslicarbazepine.
Consequence	Mean eslicarbazepine clearance values can be increased by 12 % while mean eslicarbazepine plasma levels can be decreased by 12 % [1]. During combination therapy, carbamazepine enhances eslicarbazepine adverse effects including diplopia, abnormal coordination, and dizziness. These effects are probably the consequence of a pharmacodynamic interaction [2].
Clobazam	Clobazam does not affect the pharmacokinetics of eslicarbazepine [1].
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	Gabapentin does not affect the pharmacokinetics of eslicarbazepine [1].
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of eslicarbazepine [3].
Levetiracetam	Does not affect the pharmacokinetics of eslicarbazepine [1].

Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Oxcarbazepine	Oxcarbazepine and eslicarbazepine acetate in combination are contraindicated.
Phenobarbital	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenytoin	Enhances the metabolism of eslicarbazepine.
Consequence	Plasma eslicarbazepine AUC values can decrease by 31–33 %. The interaction is considered to be the consequence of induction of eslicarbazepine metabolism most likely of glucuronidation [1, 4].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Enhances the metabolism of eslicarbazepine.
Consequence	In healthy volunteers, eslicarbazepine mean plasma C_{\max} and AUC values are decreased by 13 and 7 %, respectively [5]. In contrast, population pharmacokinetic data indicate that topiramate does not affect the pharmacokinetics of eslicarbazepine [1].
Valproic acid	Does not affect the pharmacokinetics of eslicarbazepine [1].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Ethosuximide

Ethosuximide (Fig. 1) corresponds chemically to 2-ethyl-2-methylsuccinimide with an empirical formula of $C_7H_{11}NO_2$ and a molecular weight of 141.7.

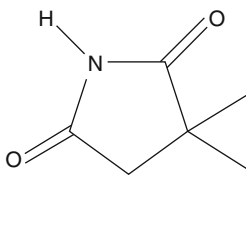


FIGURE 1 Ethosuximide

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, ethosuximide is rapidly absorbed (T_{\max} = 1–4 h) with a bioavailability of >90 %. Its volume of distribution is 0.7 L/kg, and plasma protein binding is 0 %.

Biotransformation

Ethosuximide is extensively metabolized in the liver by hydroxylation (primarily by CYP3A and to a lesser extent by CYP2E and CYP2B/C) to form isomers of 2-(1-hydroxyethyl)-2-methylsuccinimide, of which at least 40 % are glucuronide conjugates.

Renal Excretion

Approximately 20 % of an administered dose is excreted as unchanged ethosuximide in urine.

Elimination

Plasma elimination half-life values of ethosuximide are 40–60 h in adults and 30–40 h in children. In patients co-prescribed with enzyme-inducing antiepileptic drugs half-life values are 20–40 h.

Time to new steady-state ethosuximide blood levels consequent to an inhibition of metabolism interaction:

- Adults = 8–12 days later
- Children = 6–8 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of ethosuximide on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on ethosuximide monotherapy is most likely to occur at ethosuximide plasma levels of 40–100 mg/L (300–700 $\mu\text{mol/L}$). The conversion factor

from mg/L to $\mu\text{mol/L}$ for ethosuximide is 7.06 (i.e., $1 \text{ mg/L} = 7.06 \mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic interactions

- Ethosuximide affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of ethosuximide – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine Consequence	Enhances the metabolism of ethosuximide. Mean plasma ethosuximide AUC values can be decreased by 49 %. The interaction is the consequence of induction of ethosuximide metabolism through CYP3A [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of ethosuximide [2].
Levetiracetam	Does not affect the pharmacokinetics of ethosuximide [3].
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital	Enhances the metabolism of ethosuximide.
Consequence	Mean plasma ethosuximide AUC values can be decreased by 49 %. The interaction is the consequence of induction of ethosuximide metabolism through CYP3A [1].
Phenytoin	Enhances the metabolism of ethosuximide.
Consequence	Mean plasma ethosuximide AUC values can be decreased by 49 %. The interaction is the consequence of induction of ethosuximide metabolism through CYP3A [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	Enhances the metabolism of ethosuximide.
Consequence	The mean level/dose ratio for ethosuximide is decreased by 33 % [4].

Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	Inhibits the metabolism of ethosuximide.
Consequence	Ethosuximide blood levels will increase [5].
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Valproic acid	Conflicting effects have been reported.
Consequence	Plasma ethosuximide levels are reported to decrease, increase, and not change during coadministration with valproic acid [4, 6]. During combination therapy, valproic acid synergistically enhances the antiepileptic efficacy (absence seizures) and toxicity of ethosuximide. These effects are probably the consequence of a pharmacodynamic interaction [7].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Felbamate

Felbamate (Fig. 1) corresponds chemically to 2-phenyl-1,3-propanediol dicarbamate with an empirical formula of $C_{11}H_{14}N_2O_4$ and a molecular weight of 238.24.

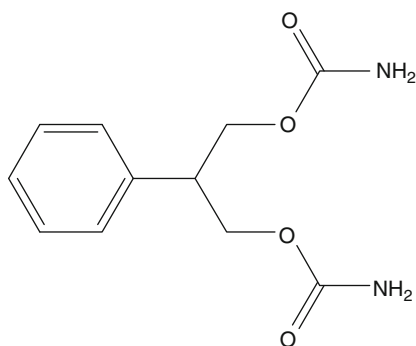


FIGURE 1 Felbamate

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, felbamate is rapidly absorbed ($T_{\max} = 2-6$ h) with a bioavailability of >90 %. Its volume of distribution is 0.7–0.91 L/kg, and plasma protein binding is 25 %.

Biotransformation

Only 50 % of an administered dose is metabolized in the liver, by CYP3A4 and CYP2E1, to form two hydroxylated metabolites (*para*-hydroxyfelbamate and 2-hydroxyfelbamate – 10–15 %) and a variety of other unidentified polar metabolites, some of them being glucuronides or sulfate esters. The atropaldehyde (2-phenylpropenal) metabolite may contribute to the cytotoxicity seen in some patients treated with felbamate.

Renal Excretion

Approximately 50 % of an administered dose is excreted as unchanged felbamate in urine.

Elimination

In adult volunteers, plasma elimination half-life values are 16–22 h while in patients co-prescribed with enzyme-inducing antiepileptic drugs half-life values are 10–18 h.

Time to new steady-state felbamate blood levels consequent to an inhibition of metabolism interaction:

- Adults = 3–5 days later

Effects on Isoenzymes

At therapeutic concentrations, felbamate *in vitro* inhibits the activity of CYP2C19. Consequently, pharmacokinetic

interactions of metabolic origin with other antiepileptic drugs and other medicines can be expected.

Felbamate has no in vitro inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4.

No in vitro data on the induction potential of felbamate on human CYP enzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on felbamate monotherapy is most likely to occur at plasma felbamate levels of 30–60 mg/L (125–250 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for felbamate is 4.20 (i.e., 1 mg/L = 4.20 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Felbamate affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of felbamate – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine Consequence	Enhances the metabolism of felbamate. Mean plasma felbamate levels can decrease by 17 %. The interaction is the consequence of induction of felbamate metabolism through CYP3A4 [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	Does not affect the pharmacokinetics of felbamate [2].

Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Gabapentin Consequence	Decreases the elimination of felbamate. The mean plasma elimination half-life of felbamate can be increased by 46 % and mean plasma clearance decreased by 37 %. This interaction is considered to occur at the level of renal excretion [3].
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of felbamate [4].
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Oxcarbazepine	Does not affect the pharmacokinetics of felbamate [5].
Phenobarbital	Does not affect the pharmacokinetics of felbamate [6].
Phenytoin Consequence	Enhances the metabolism of felbamate. Mean plasma felbamate levels can decrease by 51 %. The interaction is the consequence of induction of felbamate metabolism through CYP3A4 [2].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction similar to that seen with phenobarbital can be expected.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Valproic acid Consequence	Inhibits the metabolism of felbamate. Mean plasma felbamate clearance values are decreased by 21% and mean plasma felbamate levels can increase by 53% [7].
Vigabatrin	Does not affect the pharmacokinetics of felbamate [8].
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Gabapentin

Gabapentin (Fig. 1) corresponds chemically to 1-(aminomethyl)-cyclohexanecarboxylic acid with an empirical formula of $C_9H_{17}NO_2$ and a molecular weight of 171.23.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, gabapentin is rapidly absorbed ($T_{\max}=2-3$ h) with a bioavailability of <60 %. Its volume of distribution is 0.65–1.04 L/kg, and plasma protein binding is 0 %.

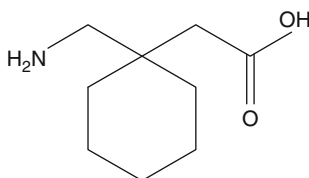


FIGURE 1 Gabapentin

Biotransformation

Gabapentin is not metabolized.

Renal Excretion

Approximately 100 % of an administered dose is excreted as unchanged gabapentin in urine.

Elimination

Following a single dose, plasma elimination half-life values in adults are 5–9 h.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of gabapentin on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on gabapentin monotherapy is most likely to occur at plasma levels of 2–20 mg/L (12–117 $\mu\text{mol/L}$). The conversion factor from mg to μmol for gabapentin is 5.84 (i.e., 1 mg/L = 5.84 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Gabapentin affects the pharmacokinetics of other drugs – does not interact.
- Other drugs affect the pharmacokinetics of gabapentin – does not interact.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Does not affect the pharmacokinetics of gabapentin [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	Does not affect the pharmacokinetics of gabapentin [2].
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	Does not affect the pharmacokinetics of gabapentin [3].
Lamotrigine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Levetiracetam	Does not affect the pharmacokinetics of gabapentin [4].
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenobarbital	Does not affect the pharmacokinetics of gabapentin [5].

Phenytoin	Does not affect the pharmacokinetics of gabapentin [6].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	Does not affect the pharmacokinetics of gabapentin [7].
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Valproic acid	Does not affect the pharmacokinetics of gabapentin [1].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Lacosamide

Lacosamide (Fig. 1) corresponds chemically to (R)-2-acetamido-*N*-benzyle-3-methoxypropamide with an empirical formula of $C_{13}H_{18}N_2O_3$ and a molecular weight of 250.29.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, lacosamide is rapidly absorbed ($T_{\max} = 1\text{--}2\text{ h}$) with a bioavailability of 100 %. Its volume of distribution is 0.6–0.7 L/kg, and plasma protein binding is <30 %.

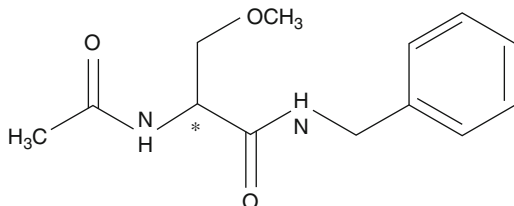


FIGURE 1 Lacosamide

Biotransformation

Lacosamide is moderately metabolized in the liver, by demethylation, to *O*-desmethyl lacosamide (30 %) and to other unidentified metabolites (30 %). The formation of *O*-desmethyl lacosamide is due to CYP2C19.

Renal Excretion

Approximately 40 % of an administered dose is excreted as unchanged lacosamide in urine.

Elimination

The plasma elimination half-life in healthy volunteers and in patients with epilepsy is 13 h.

Time to new steady-state lacosamide blood levels consequent to an inhibition of metabolism interaction:

- Adults = 2–3 days later

Effects on Isoenzymes

At therapeutic concentrations, lacosamide in vitro does not inhibit or induce the activities of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and other medicines are not expected.

Therapeutic Drug Monitoring

Optimum seizure control in patients on lacosamide monotherapy is most likely to occur at plasma lacosamide levels of

10–20 mg/L (40–80 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for lacosamide is 3.99 (i.e., 1 mg/L = 3.99 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Lacosamide affects the pharmacokinetics of other drugs – does not interact.
- Other drugs affect the pharmacokinetics of lacosamide – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Does not affect the pharmacokinetics of lacosamide [1]. Neurotoxicity may occur in combination with carbamazepine, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [2].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of lacosamide [3]. Neurotoxicity may occur in combination with lamotrigine, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [2].
Levetiracetam	Does not affect the pharmacokinetics of lacosamide [3].
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	Does not affect the pharmacokinetics of lacosamide [3]. Neurotoxicity may occur in combination with oxcarbazepine, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [2].
Phenobarbital	Enhances the metabolism of lacosamide.
Consequence	Mean plasma lacosamide AUC values are decreased by ~30 % [4].
Phenytoin	Enhances the metabolism of lacosamide.
Consequence	Mean plasma lacosamide AUC values are decreased by ~20 % [4]. Neurotoxicity may occur in combination with phenytoin, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [2].

Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Does not affect the pharmacokinetics of lacosamide [3].
Valproic acid	Does not affect the pharmacokinetics of lacosamide [5].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Lamotrigine

Lamotrigine (Fig. 1) corresponds chemically to 3,5-diamino-6[2,3-dichlorophenyl]-1,2,4-triazine with an empirical formula of $C_9H_7Cl_2N_5$ and a molecular weight of 256.09.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, lamotrigine is rapidly absorbed ($T_{\max} = 1\text{--}3\text{ h}$) with a bioavailability of $\geq 95\%$. Its volume of distribution is $0.9\text{--}1.3\text{ L/kg}$, and plasma protein binding is 55% .

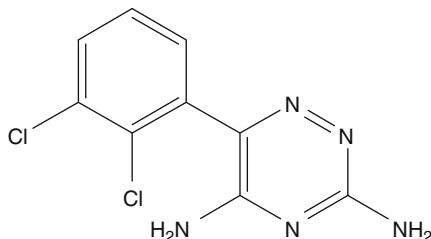


FIGURE 1 Lamotrigine

Biotransformation

Lamotrigine undergoes extensive metabolism in the liver, by conjugation with glucuronic acid, to various metabolites including 2-*N*-glucuronide (76 % of dose) and 5-*N*-glucuronide (10 % of dose), a 2-*N*-methyl metabolite (0.14 % of dose), and other unidentified minor metabolites (4 % of dose). Glucuronidation is primarily via UGT1A4, but UGT1A1 and UGT2B7 also contribute. Lamotrigine undergoes autoinduction so that clearance can increase by 17–37 %, and this may require an upward dosage adjustment, particularly when prescribed as monotherapy.

Renal Excretion

Approximately 10 % of an administered dose is excreted as unchanged lamotrigine in urine.

Elimination

In the absence of enzyme-inducing antiepileptic drugs, plasma elimination half-life values in adults are 15–35 h while in the presence of enzyme-inducing antiepileptic drugs, half-life values are 8–20 h. In the absence of enzyme-inducing antiepileptic drugs, but with valproic acid comedication, half-life values are 30–90 h. In the presence of enzyme-inducing antiepileptic drugs and also with valproic acid comedication, half-life values are 15–35 h.

Time to new steady-state lamotrigine blood levels consequent to an inhibition of metabolism interaction:

- Adults = 3–7 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of lamotrigine on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on lamotrigine monotherapy is most likely to occur at plasma lamotrigine levels of 3–15 mg/L (12–58 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for lamotrigine is 3.90 (i.e., 1 mg/L = 3.90 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Lamotrigine affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of lamotrigine – moderate.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine clearance is increased by 30–50 % resulting in decreased plasma lamotrigine levels. The interaction is the consequence of induction of lamotrigine metabolism through UGT1A4 glucuronidation [1]. The high frequency of neurotoxicity observed with this drug combination represents a pharmacodynamic rather than pharmacokinetic interaction [2].
Clobazam	Does not affect the pharmacokinetics of lamotrigine [3].
Clonazepam	Does not affect the pharmacokinetics of lamotrigine [3].

Eslicarbazepine acetate	Enhances the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine C _{max} and AUC values can decrease by 13 and 14 %, respectively [4].
Ethosuximide	Does not affect the pharmacokinetics of lamotrigine [3].
Felbamate	Inhibits the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine C _{max} and AUC values can be increased by 13 and 14 %, respectively [5].
Gabapentin	Does not affect the pharmacokinetics of lamotrigine [3].
Lacosamide	Does not affect the pharmacokinetics of lamotrigine [6].
	Neurotoxicity may occur in combination with lamotrigine, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [7].
Levetiracetam	Does not affect the pharmacokinetics of lamotrigine [1].
Methsuximide	Enhances the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine levels can be decreased by 36–72 %. The interaction is the consequence of induction of lamotrigine metabolism through UGT1A4 glucuronidation [8].
Oxcarbazepine	Enhances the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine levels can be decreased by 34 %. The interaction is the consequence of induction of lamotrigine metabolism probably through UGT1A4 glucuronidation [9].
Phenobarbital	Enhances the metabolism of lamotrigine.

Consequence	Clearance can be increased by 100 %, and mean plasma lamotrigine levels can be decreased [10].
Phenytoin	Enhances the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine clearance is increased by 125 % resulting in decreased plasma lamotrigine levels. The interaction is the consequence of induction of lamotrigine metabolism through UGT1A4 glucuronidation [1]. During combination therapy with phenytoin, a drug-induced chorea can occur. This is considered to be the consequence of a pharmacodynamic interaction [11].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	Does not affect the pharmacokinetics of lamotrigine [12].
Primidone	Enhances the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine clearance can be increased by 100 %, and mean plasma lamotrigine levels can be decreased [1, 10].
Retigabine	Enhances the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine clearance can be increased by 22 %, mean plasma lamotrigine half-life values are decreased by 18 %, and mean plasma lamotrigine AUC values are decreased by 15 %. The interaction is probably the consequence of induction of retigabine metabolism through UGT1A4 [13].

Rufinamide	Enhances the metabolism of lamotrigine.
Consequence	Plasma lamotrigine clearance is increased by 8–16 % so that plasma lamotrigine levels are decreased by 7–13 %. The interaction is probably the consequence of induction of UGT1A4 [14].
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	Inhibits the metabolism of lamotrigine.
Consequence	Plasma lamotrigine levels can be increased [15].
Tiagabine	Does not affect the pharmacokinetics of lamotrigine [3].
Topiramate	Does not affect the pharmacokinetics of lamotrigine [16]. Topiramate and lamotrigine can have a synergistic anticonvulsant effect consequent to a pharmacodynamic interaction [17].
Valproic acid	Inhibits the metabolism of lamotrigine.
Consequence	Mean plasma lamotrigine clearance is decreased by 60 % resulting in increased plasma lamotrigine levels. The interaction is the consequence of inhibition of lamotrigine metabolism through UGT1A4 glucuronidation [1]. Concurrent valproic acid therapy is a risk factor for the development of skin rash with lamotrigine. The introduction of lamotrigine to patients already taking valproic acid should be undertaken with caution, using a low starting dose and a slow-dose escalation rate. However, there is no risk of rash if

valproic acid is introduced to patients already stabilized on lamotrigine [18].

During combination therapy, valproic acid synergistically enhances the antiepileptic efficacy (partial and generalized seizures) and toxicity of lamotrigine. This is considered to be the consequence of a pharmacodynamic interaction [19–21].

A case of delirium has been reported when valproic acid was added to lamotrigine. This effect is probably the consequence of a pharmacodynamic interaction [22].

Vigabatrin

Does not affect the pharmacokinetics of lamotrigine [1].

Lamotrigine and vigabatrin in combination may be associated with synergistic efficacy in patients with partial and secondary generalized tonic-clonic seizures consequent to a pharmacodynamic interaction [23].

Zonisamide

Does not affect the pharmacokinetics of lamotrigine [24].

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Levetiracetam

Levetiracetam (Fig. 1) corresponds chemically to (S)-alpha-ethyl-2 oxo-1-pyrrolidine acetamide with an empirical formula of $C_8H_{14}N_2O_2$ and a molecular weight of 170.21.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, levetiracetam is rapidly absorbed (T_{\max} = 1–2 h) with a bioavailability of ≥ 95 %. Its volume of distribution is 0.5–0.7 L/kg, and plasma protein binding is 0 %.

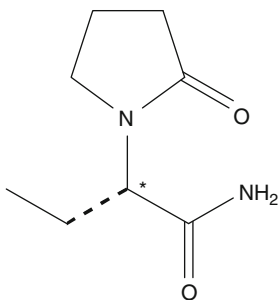


FIGURE 1 Levetiracetam

Biotransformation

Levetiracetam undergoes minimal metabolism with ~30 % of the dose metabolized by hydrolysis to a deaminated metabolite. This metabolism is independent of the hepatic cytochrome P450 system and is via a type-B esterase enzyme located in whole blood.

Renal Excretion

Approximately 66 % of an administered dose is excreted as unchanged levetiracetam in urine.

Elimination

Plasma elimination half-life values are 6–8 h in adults, 5–6 h in children, and 10–11 h in the elderly.

Effects on Isoenzymes

At therapeutic concentrations, levetiracetam has no in vitro inhibitory or induction effects on the activity of CYP1A2, CYP2C9, CYP2D6, CYP2E1, CYP3A4, CYP2A6, epoxide hydrolase, UGT1*6, UGT1*1, UGT (pl6.2), and UDT glucuro-conjugating valproic acid. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and other medicines are not expected.

Therapeutic Drug Monitoring

Optimum seizure control in patients on levetiracetam monotherapy is most likely to occur at plasma levetiracetam levels of 12–46 mg/L (70–270 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for levetiracetam is 5.88 (i.e., 1 mg/L = 5.88 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Levetiracetam affects the pharmacokinetics of other drugs – does not interact.
- Other drugs affect the pharmacokinetics of levetiracetam – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the metabolism of levetiracetam.
Consequence	The mean plasma clearance of levetiracetam is increased by 26 % so that mean AUC values are decreased by 21 %. The mean elimination half-life of levetiracetam can be decreased by 16 % [1]. A pharmacodynamic interaction may occur whereby symptoms of carbamazepine toxicity present [2].
Clobazam	Does not affect the pharmacokinetics of levetiracetam [3].
Clonazepam	Does not affect the pharmacokinetics of levetiracetam [3].
Eslicarbazepine acetate	Does not affect the pharmacokinetics of levetiracetam [4].
Ethosuximide	Does not affect the pharmacokinetics of levetiracetam [3].
Felbamate	Does not affect the pharmacokinetics of levetiracetam [5].
Gabapentin	Does not affect the pharmacokinetics of levetiracetam [3].
Lacosamide	Does not affect the pharmacokinetics of levetiracetam [6].

Lamotrigine	Enhances the metabolism of levetiracetam.
Consequence	Levetiracetam plasma levels are decreased so that the median level to dose ratio for levetiracetam is decreased by 14 % [7].
Methsuximide	Enhances the metabolism of levetiracetam.
Consequence	Levetiracetam plasma levels are decreased so that the median level to dose ratio for levetiracetam is decreased by 27 % [7].
Oxcarbazepine	Enhances the metabolism of levetiracetam.
Consequence	Levetiracetam plasma levels are decreased so that the median level to dose ratio for levetiracetam is decreased by 35 % [7].
Phenobarbital	Enhances the metabolism of levetiracetam.
Consequence	The mean plasma clearance of levetiracetam is increased by 26 % so that mean plasma AUC values are decreased by 21 %. The mean plasma elimination half-life of levetiracetam can be decreased by 16 % [1].
Phenytoin	Enhances the metabolism of levetiracetam.
Consequence	The mean plasma clearance of levetiracetam is increased by 26 % so that mean plasma AUC values are decreased by 21 %. The mean plasma elimination half-life of levetiracetam can be decreased by 16 % [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	Does not affect the pharmacokinetics of levetiracetam [8].

Primidone	Does not affect the pharmacokinetics of levetiracetam [8].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Tiagabine	Does not affect the pharmacokinetics of levetiracetam [9].
Topiramate	Does not affect the pharmacokinetics of levetiracetam [9]. A pharmacodynamic interaction may occur whereby symptoms of decreased appetite, weight loss, and nervousness present [5].
Valproic acid	Does not affect the pharmacokinetics of levetiracetam [10].
Vigabatrin	Does not affect the pharmacokinetics of levetiracetam [9].
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Methsuximide

Methsuximide (Fig. 1) corresponds chemically to *N*-2-dimethyl-2-phenyl-succinimide with an empirical formula of $C_{12}H_{13}NO_2$ and a molecular weight of 203.23.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion methsuximide is rapidly absorbed with T_{max} values of 1–4 h for the pharmacologically active metabolite *N*-desmethyldesmethsuximide. Neither its oral bioavailability nor its volume of distribution has been

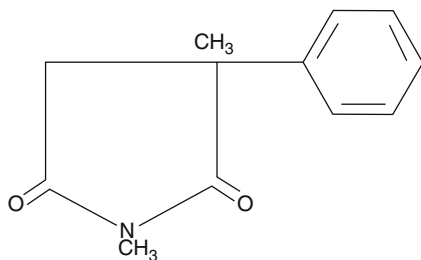


FIGURE 1 Methsuximide

established, but the plasma protein binding of *N*-desmethylnmethsuximide is 45–60 %.

Biotransformation

Methsuximide is rapidly metabolized in the liver to its primary pharmacologically active metabolite *N*-desmethylmethsuximide, which is subsequently hydroxylated by CYP2C19.

Renal Excretion

Less than 1 % of an administered dose is excreted as unchanged methsuximide in urine.

Elimination

Plasma elimination half-life values for methsuximide in adults are 1.0–2.6 h. Plasma elimination half-life values for *N*-desmethylnmethsuximide are 34–80 h in adults and 16–45 h in children.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of methsuximide on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on methsuximide monotherapy is most likely to occur at plasma *N*-desmethylnmethsuximide levels of 10–40 mg/L (50–200 µmol/L). The conversion factor from mg/L

to $\mu\text{mol/L}$ for *N*-desmethylnmethsuximide is 4.92 (i.e., $1 \text{ mg/L} = 4.92 \mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Methsuximide affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of methsuximide – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	Inhibits the metabolism of methsuximide.
Consequence	<i>N</i> -desmethylnmethsuximide (the pharmacologically active metabolite)

	of methsuximide) plasma levels are increased by 26–46 % [1].
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital	Enhances the metabolism of methsuximide.
Consequence	The plasma clearance of methsuximide is increased so that <i>N</i> -desmethylnmethsuximide/methsuximide plasma ratios are increased [2].
Phenytoin	Enhances the metabolism of methsuximide.
Consequence	The plasma clearance of methsuximide is increased so that <i>N</i> -desmethylnmethsuximide/methsuximide plasma ratios are increased [2].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Valproic acid	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Oxcarbazepine

Oxcarbazepine (Fig. 1) corresponds chemically to 10,11-dihydro-10-oxo-5H-dibenz(b,f)azepine-4-carboxamide with an empirical formula of $C_{15}H_{12}N_2O_2$ and a molecular weight of 252.27.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, oxcarbazepine is rapidly absorbed with T_{max} values of 3–6 h and with a bioavailability of 100 %. The

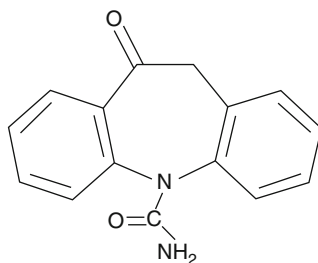


FIGURE 1 Oxcarbazepine

volume of distribution of its pharmacologically active metabolite, 10-hydroxycarbazepine, is 0.75 L/kg. The protein binding of 10-hydroxycarbazepine is 40 % while that of oxcarbazepine is 60 %.

Biotransformation

Oxcarbazepine undergoes rapid and extensive metabolism to its pharmacologically active metabolite, 10-hydroxycarbazepine (also known as licarbazepine), by stereoselective biotransformation mediated by a cytosolic, non-microsomal, and non-inducible arylketone reductase. 10-hydroxycarbazepine subsequently undergoes glucuronidation (51 %) or undergoes hydroxylation to form a dihydrodiol metabolite (28 %). Minor amounts (4 % of dose) of 10-hydroxycarbazepine are oxidized to an inactive 10,11-dihydroxy metabolite. Only the latter reaction depends on CYP isoenzymes.

Renal Excretion

Less than 1 % of an administered dose is excreted as unchanged oxcarbazepine in urine.

Elimination

The plasma elimination half-life of oxcarbazepine is ~2 h; thus, oxcarbazepine is essentially a prodrug which is rapidly converted to its pharmacologically active 10-hydroxycarbazepine metabolite. In the absence of enzyme-inducing antiepileptic drugs, plasma half-life values for 10-hydroxycarbazepine are 8–15 h, while in the presence of enzyme-inducing antiepileptic drugs half-life values are 7–12 h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Adults = 2–3 days later (10-hydroxycarbazepine)

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of 10-hydroxycarbazepine on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on oxcarbazepine monotherapy is most likely to occur at plasma 10-hydroxycarbazepine levels of 3–35 mg/L (12–137 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for 10-hydroxycarbazepine is 3.96 (i.e., 1 mg/L = 3.96 $\mu\text{mol/L}$).

During treatment with oxcarbazepine, only the pharmacologically active metabolite, 10-hydroxycarbazepine, is monitored because oxcarbazepine is very rapidly metabolized to its metabolite, and therefore, oxcarbazepine is essentially not detectable in blood by 1 h post-ingestion.

Propensity to Be Associated with Pharmacokinetic Interactions

- Oxcarbazepine affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of oxcarbazepine – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the metabolism of 10-hydroxycarbazepine.
Consequence	Median plasma 10-hydroxycarbazepine AUC values can be decreased by 35 % [1].

Clobazam	Does not affect the pharmacokinetics of 10-hydroxycarbazepine [2].
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	Eslicarbazepine acetate and oxcarbazepine in combination are contraindicated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	Does not affect the pharmacokinetics of 10-hydroxycarbazepine [3].
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	Enhances the metabolism of 10-hydroxycarbazepine.
Consequence	Mean plasma 10-hydroxycarbazepine levels can be decreased by 15 % [4]. Neurotoxicity may occur in combination with oxcarbazepine, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [5].
Lamotrigine	Does not affect the pharmacokinetics of 10-hydroxycarbazepine [6].
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenobarbital	Enhances the metabolism of 10-hydroxycarbazepine.
Consequence	Mean plasma 10-hydroxycarbazepine AUC values can decrease by 25 % [7].

Phenytoin	Enhances the metabolism of 10-hydroxycarbazepine.
Consequence	Mean plasma 10-hydroxycarbazepine AUC values can decrease by 32 % [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, an interaction similar to that seen with phenobarbital can be expected.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Does not affect the pharmacokinetics of 10-hydroxycarbazepine [6].
Valproic acid	Does not affect the pharmacokinetics of 10-hydroxycarbazepine [7]. Valproic acid displaces 10-hydroxycarbazepine from its plasma protein binding sites. [8].
Consequence	During combination therapy with valproic acid, 10-hydroxycarbazepine

binding is 36 % versus 47 % for monotherapy oxcarbazepine. Clinical management may best be guided by monitoring free blood levels of 10-hydroxycarbazepine [8].

Vigabatrin

The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Zonisamide

The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Phenobarbital

Phenobarbital (Fig. 1) corresponds chemically to 5-ethyl-5-phenylbarbituric acid with an empirical formula of $C_{12}H_{12}N_2O_3$ and a molecular weight of 232.23.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, phenobarbital is rapidly absorbed ($T_{\max} = 2-4$ h) with a bioavailability of >90 %. Its volume of

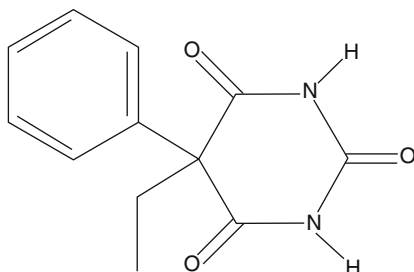


FIGURE 1 Phenobarbital

distribution is 0.61 L/kg in adult and ~1.0 L/kg in newborns, and plasma protein binding is 55 %.

Biotransformation

Phenobarbital is extensively metabolized in the liver to two major metabolites, *p*-hydroxyphenobarbital, which partially undergoes sequential metabolism to a glucuronic acid conjugate, and 9- β -glucopyranosylphenobarbital, an *N*-glucoside conjugate. CYP2C9 plays a major role in the metabolism of phenobarbital to *p*-hydroxyphenobarbital with minor metabolism by CYP2C19 and CYP2E1. Phenobarbital is an enzyme inducer. Phenobarbital undergoes autoinduction so that its clearance can increase, and this may require an upward dosage adjustment when prescribed as monotherapy.

Renal Excretion

In adults, 20–25 % of an administered dose is excreted as unchanged phenobarbital in urine.

Elimination

Plasma elimination half-life values are 70–140 h in adults while in newborns, half-life values are 100–200 h. During the neonatal period, phenobarbital elimination accelerates markedly; thereafter, half-life values are very short, with average values of 63 h during the first year of life and 69 h at ages 1–5 years.

Time to new steady-state phenobarbital blood levels consequent to an inhibition of metabolism interaction:

- Adults = 15–29 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of phenobarbital on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on phenobarbital monotherapy is most likely to occur at plasma phenobarbital levels of 10–40 mg/L (43–172 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for phenobarbital is 4.31 (i.e., 1 mg/L = 4.31 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Phenobarbital affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of phenobarbital – substantial.

Interactions with AEDs

Acetazolamide	Inhibits the metabolism of phenobarbital.
Consequence	Plasma phenobarbital levels can be increased [1].
Carbamazepine	Does not affect the pharmacokinetics of phenobarbital [2].
Clobazam	Does not affect the pharmacokinetics of phenobarbital [3].
Clonazepam	Does not affect the pharmacokinetics of phenobarbital [4].

Eslicarbazepine acetate	Does not affect the pharmacokinetics of phenobarbital [5].
Ethosuximide	Does not affect the pharmacokinetics of phenobarbital [6].
Felbamate	Inhibits the metabolism of phenobarbital.
Consequence	Mean plasma phenobarbital levels can be increased by 24 %. The interaction is the consequence of inhibition of CYP2C19 [7].
Gabapentin	Does not affect the pharmacokinetics of phenobarbital [8].
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of phenobarbital [9].
Levetiracetam	Does not affect the pharmacokinetics of phenobarbital [10].
Methsuximide	Inhibits the metabolism of phenobarbital.
Consequence	Plasma phenobarbital levels can be increased by 23–57 %. The interaction is considered to be the consequence of inhibition of CYP2C19 [11].
Oxcarbazepine	Inhibits the metabolism of phenobarbital.
Consequence	At oxcarbazepine dosages above 1,200 mg/day, mean plasma phenobarbital levels can be increased by 15 %. The interaction is the consequence of inhibition of CYP2C19 [12].
Phenytoin	Inhibits the metabolism of phenobarbital.
Consequence	Plasma phenobarbital levels can be increased by 50–70 %. The interaction is the consequence of inhibition of CYP2C19 [13].

Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	Does not affect the pharmacokinetics of phenobarbital [14].
Primidone	Not commonly co-prescribed.
Retigabine	Inhibits the metabolism of phenobarbital.
Consequence	Mean plasma clearance of phenobarbital can be decreased by 3 %, and mean plasma AUC values are increased by 4 % [15].
Rufinamide	Inhibits the metabolism of phenobarbital.
Consequence	Plasma clearance of phenobarbital is decreased by 7–12 % so that plasma phenobarbital levels are increased by 8–13 % [16].
Stiripentol	Inhibits the metabolism of phenobarbital.
Consequence	Plasma clearance of phenobarbital is decreased by 30–40 % so that plasma phenobarbital levels are increased. The interaction is the consequence of inhibition of CYP2C9 and CYP2C19 [17].
Sulthiame	Inhibits the metabolism of phenobarbital.
Consequence	Plasma phenobarbital levels can be increased [18].
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Does not affect the pharmacokinetics of phenobarbital [19].
Valproic acid	Inhibits the metabolism of phenobarbital.
Consequence	The extent of this interaction is characterized by considerable interindividual

variability with 30–50 % increases in mean plasma phenobarbital levels, probably via an action on CYP2C9 and/or CYP2C19. In children, mean plasma phenobarbital levels can be increased by 112 % [20].

Vigabatrin

Does not affect the pharmacokinetics of phenobarbital [21].

During combination therapy for the treatment of infantile spasms, especially in patients with tuberous sclerosis, phenobarbital appears to delay or prevent the onset of seizure control by vigabatrin. This is considered to be the consequence of a pharmacodynamic interaction [22].

Zonisamide

Does not affect the pharmacokinetics of phenobarbital [23].

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Phenytoin

Phenytoin (Fig. 1) corresponds chemically to 5,5-diphenyl-2,4-imidazolidinedione with an empirical formula of $C_{15}H_{12}N_2O_2$ and a molecular weight of 252.26 for the free acid and a molecular weight of 274.25 for the sodium salt which is equivalent to an acid content of 91.98 %.

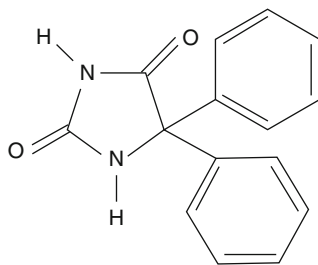


FIGURE 1 Phenytoin

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, phenytoin's rate of absorption (T_{\max} = 4–12 h) and bioavailability (≥ 80 %) are formulation-dependent. Its volume of distribution is 0.5–0.8 L/kg, and plasma protein binding is 90 %.

Biotransformation

Phenytoin undergoes extensive metabolism in the liver by hydroxylation to various metabolites, the principal metabolites being 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (p-HPPH; 67–88 %) and a dihydrodiol derivative (7–11 %). The isoenzymes responsible for the hydroxylation of phenytoin are CYP2C9 (~80 %) and CYP2C19 (~20 %). In excess of 60 % of p-HPPH is subsequently glucuronidated and excreted in urine. Phenytoin is an enzyme inducer, and additionally, phenytoin undergoes autoinduction, primarily via CYP2C19, so that its clearance can increase and this may require an upward dosage adjustment when prescribed as monotherapy.

Renal Excretion

Approximately 5 % of an administered dose is excreted as unchanged phenytoin in urine.

Elimination

In the absence of enzyme-inducing antiepileptic drugs, plasma elimination half-life values are 30–100 h while in the presence of enzyme-inducing antiepileptic drugs, half-life values are 30–100 h.

Phenytoin elimination follows Michaelis-Menten (saturable, zero-order) kinetics so that plasma half-life and clearance are dose-dependent with values decreasing with increasing dose. As a result, phenytoin steady-state plasma levels increase more than proportionately after a dose increment.

Time to new steady-state phenytoin blood levels consequent to an inhibition of metabolism interaction:

- Adults = 6–21 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of phenytoin on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on phenytoin monotherapy is most likely to occur at plasma phenytoin levels of 10–20 mg/L (40–80 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for phenytoin is 3.96 (i.e., 1 mg/L = 3.96 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Phenytoin affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of phenytoin – substantial.

Interactions with AEDs

Acetazolamide	Inhibits the metabolism of phenytoin.
Consequence	Plasma phenytoin levels can increase [1].

Carbamazepine Consequence	Conflicting results are observed. Plasma phenytoin levels may decrease, remain the same, or increase after addition of carbamazepine. This is a consequence of intersubject variability in CYP isoenzyme expression of CYP2C19 which carbamazepine inhibits and the fact that carbamazepine may increase the clearance of phenytoin through induction of CYP2C9 and/or CYP2C19 [2].
Clobazam Consequence	Inhibits the metabolism of phenytoin. Plasma phenytoin levels can be increased by 25–74 % [3].
Clonazepam Consequence	Conflicting results are observed. Plasma phenytoin levels may decrease, remain the same, or increase after addition of clonazepam. This may be the consequence of a multi-mechanism interaction, whereby clonazepam induces the metabolism of phenytoin in some patients while in other patients, it acts as an inhibitor of phenytoin metabolism [4, 5].
Eslicarbazepine acetate Consequence	Inhibits the metabolism of phenytoin. Plasma phenytoin AUC values can increase by 30–35 %. The interaction is considered to be the consequence of inhibition of CYP2C19 [6].
Ethosuximide	Does not affect the pharmacokinetics of phenytoin.
Felbamate Consequence	Inhibits the metabolism of phenytoin. Mean plasma phenytoin levels can be increased by 34, 67, and 106 % at 1,200, 1,800 and 2,400 mg/day felbamate, respectively. The interaction is the consequence of inhibition of phenytoin metabolism through CYP2C19 [7].

Gabapentin	Does not affect the pharmacokinetics of phenytoin [8].
Lacosamide	Does not affect the pharmacokinetics of phenytoin [9]. Neurotoxicity may occur in combination with phenytoin, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [10].
Lamotrigine	Does not affect the pharmacokinetics of phenytoin [11]. During combination therapy with lamotrigine, a drug-induced chorea can occur. This is considered to be the consequence of a pharmacodynamic interaction [12].
Levetiracetam	Does not affect the pharmacokinetics of phenytoin [13].
Methsuximide Consequence	Inhibits the metabolism of phenytoin. Plasma phenytoin levels can be increased by 47–102 %. The interaction is considered to be the consequence of inhibition of CYP2C19 [14].
Oxcarbazepine Consequence	Inhibits the metabolism of phenytoin. At oxcarbazepine dosages above 1,200 mg/day, mean plasma phenytoin levels can be increased by 40 %. The interaction is the consequence of inhibition of CYP2C19 [15].
Phenobarbital Consequence	Conflicting results are observed. Plasma phenytoin levels have been reported to increase, decrease, or not change upon the addition of phenobarbital. This variability reflects the fact that phenobarbital is both a CYP enzyme inducer and an inhibitor. In most patients, only small changes in blood levels occur, and no dosage

	modification is needed. However, because of variability in the magnitude and direction of the interaction, clinical response and plasma phenytoin levels should be monitored [16, 17].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	Does not affect the pharmacokinetics of phenytoin [18].
Primidone	Does not affect the pharmacokinetics of phenytoin [19].
Retigabine	Does not affect the pharmacokinetics of phenytoin [20].
Rufinamide Consequence	Inhibits the metabolism of phenytoin. Plasma clearance of phenytoin is decreased by 6–17 % so that plasma phenytoin levels are increased [21].
Stiripentol Consequence	Inhibits the metabolism of phenytoin. Plasma clearance of phenytoin is decreased by 78 % so that plasma phenytoin levels are increased. The interaction is the consequence of inhibition of CYP2C9 and CYP2C19 [22].
Sulthiame Consequence	Inhibits the metabolism of phenytoin. Mean plasma phenytoin levels can increase by 74 % [23, 24].
Tiagabine	Does not affect the pharmacokinetics of phenytoin [25].
Topiramate Consequence	Inhibits the metabolism of phenytoin. The magnitude of the interaction is variable with plasma phenytoin levels increasing by up to 25 % in some patients. At high phenytoin concentrations, where CYP2C19 contributes to phenytoin metabolism more than at low concentra-

Valproic acid
Consequence

tions, topiramate may inhibit the CYP2C19 minor metabolic pathway [26]. Conflicting results are observed. The effect of valproic acid on plasma phenytoin levels varies among patients and may vary in the same patient during the course of therapy. Thus, a persistent fall, a transient fall, or even a rise can occur in some patients. These effects are the consequence of a displacement of phenytoin from its plasma protein (albumin) binding sites and the concurrent inhibition of CYP2C9 metabolism. The free fraction of phenytoin is increased. Clinically, the need to adjust phenytoin dosage is rare, but if adjustment is necessary, it might best be guided by measurement of free (nonprotein bound) phenytoin levels [27, 28].

Vigabatrin
Consequence

Plasma phenytoin levels are decreased. During comedication with vigabatrin, mean plasma phenytoin levels can decrease by 32 %. The mechanism of this interaction is not known but does not involve any absorption, metabolic, or bioavailability processes [29].

Zonisamide

Does not affect the pharmacokinetics of phenytoin [30].

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Piracetam

Piracetam (Fig. 1) corresponds chemically to 2-oxo-1-pyrrolidine acetamide with an empirical formula of $C_6H_{10}N_2O_2$ and a molecular weight of 142.2.

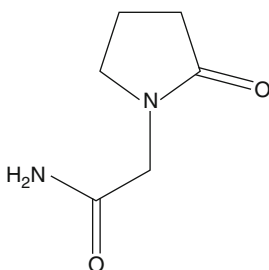


FIGURE 1 Piracetam

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, piracetam is rapidly absorbed ($T_{\max}=0.5\text{--}1.5\text{ h}$) with a bioavailability of 100 %. Its volume of distribution is 0.6 L/kg and plasma protein binding is 0 %.

Biotransformation

Piracetam is not metabolized.

Renal Excretion

Approximately 100 % of an administered dose is excreted as unchanged piracetam in urine.

Elimination

Following a single dose, plasma elimination half-life values in young men are 4–6 h.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of piracetam on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

There are no data relating plasma piracetam levels with that of seizure suppression or adverse effects.

Propensity to Be Associated with Pharmacokinetic Interactions

- Piracetam affects the pharmacokinetics of other drugs – does not interact.
- Other drugs affect the pharmacokinetics of piracetam – does not interact.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Does not affect the pharmacokinetics of piracetam [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	Does not affect the pharmacokinetics of piracetam [2].
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Lamotrigine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenobarbital	Does not affect the pharmacokinetics of piracetam [1].
Phenytoin	Does not affect the pharmacokinetics of piracetam [1].
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	Does not affect the pharmacokinetics of piracetam [2].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Valproic acid	Does not affect the pharmacokinetics of piracetam [2].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Pregabalin

Pregabalin (Fig. 1) corresponds chemically to *S*-3-(amino-methyl)-5-methylhexanoic acid with an empirical formula of $C_8H_{17}NO_2$ and a molecular weight of 159.2.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, pregabalin is rapidly absorbed ($T_{\max} = 1-2$ h) with a bioavailability of ≥ 90 %. Its volume of distribution is 0.57 L/kg, and plasma protein binding is 0 %.

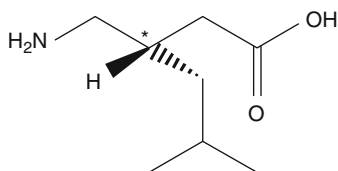


FIGURE 1 Pregabalin

Biotransformation

Pregabalin is not metabolized.

Renal Excretion

Approximately 98 % of an administered dose is excreted as unchanged pregabalin in urine.

Elimination

Following a single dose, plasma elimination half-life values in adults are 5–7 h.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of pregabalin on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Very little information is available regarding therapeutic plasma concentrations of pregabalin. However, one report states that in samples collected at random times relative to dose from patients maintained on 600 mg/day, serum pregabalin concentrations ranged from 0.9 to 14.2 mg/L (5.6–89.2 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for pregabalin is 6.28 (1 mg/L = 6.28 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Pregabalin affects the pharmacokinetics of other drugs – does not interact.

- Other drugs affect the pharmacokinetics of pregabalin – does not interact.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Does not affect the pharmacokinetics of pregabalin [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Gabapentin Consequence	Pregabalin plasma levels are decreased. Pregabalin Cmax values are decreased by 18 % [2].
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of pregabalin [1].
Levetiracetam	Does not affect the pharmacokinetics of pregabalin [3].
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenobarbital	Does not affect the pharmacokinetics of pregabalin [4].
Phenytoin Consequence	Pregabalin plasma levels are decreased. Pregabalin mean C_{\max} and AUC values are decreased by ~30 and 14 %, respectively. However, this is thought to be an effect of food co-ingestion [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Does not affect the pharmacokinetics of pregabalin [5].
Valproic acid	Does not affect the pharmacokinetics of pregabalin [1].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Zonisamide

The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Primidone

Primidone (Fig. 1) corresponds chemically to 5-ethyl-5-phenyl-4,6(1H,5H)pyrimidine-dione with an empirical formula of $C_{12}H_{14}N_2O_2$ and a molecular weight of 218.25.

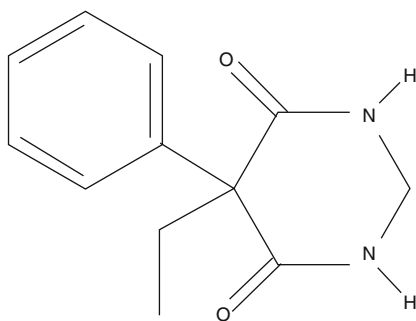


FIGURE 1 Primidone

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, primidone is rapidly absorbed (T_{\max} = 2–4 h, adults; 4–6 h children) with a bioavailability of >90 %. Its volume of distribution is 0.5–0.8 L/kg, and plasma protein binding is 10 %.

Biotransformation

Primidone is extensively metabolized in the liver by cleavage of the pyrimidine ring and oxidation of the methylene group to form, respectively, two primary metabolites, namely, phenylethylmalonamide (PEMA) and phenobarbital. Phenobarbital subsequently undergoes metabolism to two metabolites, *p*-hydroxyphenobarbital and 9- β -glucopyranosylphenobarbital. Both phenobarbital and PEMA are pharmacologically active. Primidone, via its metabolite phenobarbital, is an enzyme inducer, and additionally, phenobarbital undergoes autoinduction so that its clearance can increase and this may require an upward dosage adjustment of primidone.

Renal Excretion

Approximately 65 % of an administered dose is excreted as unchanged primidone in urine.

Elimination

In the absence of enzyme-inducing antiepileptic drugs, plasma elimination half-life values in adults are 7–22 h while in the presence of enzyme-inducing antiepileptic drugs, half-life values are 3–12 h. In newborns, half-life values are 8–80 h, and in children, they are 5–11 h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Primidone = 2–4 days later
- Phenobarbital (derived) = 15–29 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of primidone on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on primidone monotherapy is most likely to occur at primidone plasma levels of 5–10 mg/L (23–46 $\mu\text{mol/L}$) and phenobarbital plasma levels of 10–40 mg/L (43–172 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for primidone is 4.59 (1 mg/L = 4.59 $\mu\text{mol/L}$), and for phenobarbital, it is 4.31 (i.e., 1 mg/L = 4.31 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Primidone affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of primidone – substantial.

Interactions with AEDs

Acetazolamide	Decreases plasma primidone levels.
Consequence	Acetazolamide decreases the absorption of primidone so that plasma primidone levels are low or not detectable [1].

Carbamazepine Consequence	Enhances the metabolism of primidone. Carbamazepine can decrease the mean plasma primidone level to dose ratio by 17 % and increase mean plasma phenobarbital to primidone ratio by 59 % [2].
Clobazam Consequence	Inhibits the metabolism of primidone. Clobazam decreases the plasma clearance of primidone so that plasma primidone levels are increased [3].
Clonazepam	Does not affect the pharmacokinetics of primidone [4].
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide Consequence	Inhibits the metabolism of primidone. Ethosuximide can increase the mean plasma primidone level to dose ratio by 7 % but does not affect the mean plasma phenobarbital to primidone ratio [2].
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of primidone [5].
Levetiracetam	Does not affect the pharmacokinetics of primidone [6].
Methsuximide	The metabolism of primidone to phenobarbital is unaffected, but the subsequent metabolism of phenobarbital is inhibited.

Consequence	Methsuximide may cause a 17 % increase in plasma phenobarbital levels. The interaction is considered to be the consequence of inhibition of phenobarbital metabolism through CYP2C9 [7].
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital	Combination not commonly co-prescribed.
Phenytoin	Enhances the metabolism of primidone.
Consequence	Mean plasma primidone levels can decrease by 33 %, and mean plasma phenobarbital levels can increase by 112 % [8].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	Inhibits the metabolism of primidone. The metabolism of the derived phenobarbital is also inhibited.
Consequence	The plasma clearance of phenobarbital is decreased by >48 % so that plasma phenobarbital levels are increased. The interaction is the consequence of inhibition of CYP2C9 and CYP2C19 [9].
Sulthiame	The metabolism of primidone to phenobarbital is unaffected, but the subsequent metabolism of phenobarbital is inhibited.

Consequence	Sulthiame may increase plasma phenobarbital levels [10]. During combination therapy, sulthiame adverse effects such as dizziness, uncertain gate, and drowsiness may be enhanced. This is considered to be the consequence of a pharmacodynamic interaction [10].
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Does not affect the pharmacokinetics of primidone [11].
Valproic acid	The metabolism of primidone to phenobarbital is unaffected, but the subsequent metabolism of phenobarbital is inhibited.
Consequence	Mean plasma phenobarbital levels can increase by 51 %, probably via an action on CYP2C9 and/or CYP2C19, but plasma primidone levels are unaffected [12].
Vigabatrin	Does not affect the pharmacokinetics of primidone [13].
Zonisamide	Does not affect the pharmacokinetics of primidone [14].

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Retigabine

Retigabine (Fig. 1) corresponds chemically to ethyl *N*-[2-amino-4-[(4-fluorophenyl)methylamino]phenyl] carbamate with an empirical formula of $C_{16}H_{18}FN_3O_2$ and a molecular weight of 303.33.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, retigabine is rapidly absorbed ($T_{\max}=0.6\text{--}1.5\text{ h}$) with a bioavailability of ~60 %. Its volume of distribution is 2–3 L/kg, and plasma protein binding is ~80 %.

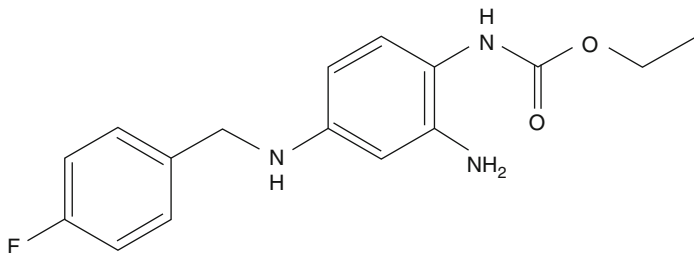


FIGURE 1 Retigabine

Biotransformation

Retigabine undergoes moderate metabolism (50–65 %) in the liver by hydrolysis/N-acetylation and glucuronidation, the major metabolite being an *N*-acetyl derivative. The isoenzymes responsible for the glucuronidation of retigabine and the *N*-acetyl metabolite are UGT1A1, UGT1A3, UGT1A4, and UGT1A9. The principal isoenzyme is UGT1A4.

Renal Excretion

Approximately 20–30 % of an administered dose is excreted as unchanged retigabine in urine.

Elimination

Plasma elimination half-life values for retigabine in adults are 8–10 h.

Time to new steady-state retigabine blood levels consequent to an inhibition of metabolism interaction:

- Adults = 2 days later

Effects on Isoenzymes

At therapeutic concentrations, retigabine has no in vitro inhibitory effects on the activity of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and medicines are not expected.

Retigabine has no in vitro induction effects on the activity of CYP1A2 or CYP3A4/5.

Therapeutic Drug Monitoring

There are no data relating plasma retigabine levels with that of seizure suppression or adverse effects.

Propensity to Be Associated with Pharmacokinetic Interactions

- Retigabine affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of retigabine – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine Consequence	Enhances the metabolism of retigabine. Clearance of retigabine is increased, and retigabine plasma levels are decreased [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Lamotrigine Consequence	Inhibits the metabolism of retigabine. Mean plasma clearance of retigabine is decreased by 13 %, mean half-life values are increased by 7.5 %, and mean AUC values are increased by 15 %. The interaction is probably the consequence of inhibition of retigabine metabolism through UGT1A4, although competition for renal elimination is also a potential mechanism [2].
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital Consequence	Inhibits the metabolism of retigabine. Mean plasma clearance of retigabine is decreased by 8 %, mean half-life values are increased by 13 %, and mean AUC values are increased by 27 %. The interaction is probably the consequence of inhibition of retigabine metabolism through UGT1A4 [3].
Phenytoin Consequence	Enhances the metabolism of retigabine. Clearance of retigabine is increased, and retigabine plasma levels are decreased [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Does not affect the pharmacokinetics of retigabine [1].
Valproic acid	Does not affect the pharmacokinetics of retigabine [1].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Rufinamide

Rufinamide (Fig. 1) corresponds chemically to 1-[(2,6-difluorophenyl) methyl]-1-hydro-1,2,3-triazole-4carboxamide with an empirical formula of $C_{10}H_8F_2N_4O$ and a molecular weight of 238.19.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, rufinamide is rapidly absorbed (T_{\max} = 4–6 h) with a bioavailability of at least 85 %. Its volume of distribution is 0.71–1.14 L/kg, and plasma protein binding is 35 %.

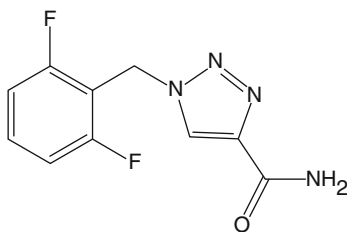


FIGURE 1 Rufinamide

Biotransformation

Rufinamide is extensively metabolized in the liver, primarily by hydrolysis mediated by carboxylesterases, to a carboxylic acid derivative CGP 47292. Acyl glucuronide metabolites of CGP 47292 constitute a minor component.

Renal Excretion

Approximately 2 % of an administered dose is excreted as unchanged rufinamide in urine.

Elimination

Plasma elimination half-life values for rufinamide in adults are 6–10 h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction

- Adults = 1–2 days later

Effects on Isoenzymes

At therapeutic concentrations, rufinamide in vitro has no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D, CYP2E1, CYP3A4/5, and CYP4A9/11. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and other medicines are not expected.

No in vitro data on the induction potential of rufinamide on human CYP enzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on rufinamide monotherapy is most likely to occur at plasma levels of 30–40 mg/L (126–168 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for rufinamide is 4.20 (i.e., 1 mg/L = 4.20 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Rufinamide affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of rufinamide – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the metabolism of rufinamide.
Consequence	Steady-state rufinamide levels can decrease by 19–26 %. This interaction is more substantial in children [1].
Clobazam	Does not affect the pharmacokinetics of rufinamide [1].
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	Does not affect the pharmacokinetics of rufinamide [2].
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	Does not affect the pharmacokinetics of rufinamide [1].
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	Enhances the metabolism of rufinamide.
Consequence	Mean rufinamide plasma levels can decrease by 29 % [3].
Oxcarbazepine	Enhances the metabolism of rufinamide.
Consequence	Mean rufinamide plasma levels can decrease by 21 % [3].
Phenobarbital	Enhances the metabolism of rufinamide.
Consequence	Steady-state rufinamide levels can decrease by 25–46 %. This interaction is more substantial in children [1].
Phenytoin	Enhances the metabolism of rufinamide.
Consequence	Steady-state rufinamide levels can decrease by 25–46 %. This interaction is more substantial in children [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	Enhances the metabolism of rufinamide.
Consequence	Steady-state rufinamide levels can decrease by 25–46 %. This interaction is more substantial in children [1].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	Does not affect the pharmacokinetics of rufinamide [1].
Valproic acid	Inhibits the metabolism of rufinamide.
Consequence	The interaction is more marked in children, and typically, rufinamide plasma levels can increase by 55–70 %. Rufinamide plasma levels can increase by ≤ 26 and < 16 % in adolescents and adults, respectively. The difference in magnitude of this interaction can be explained by the observation that plasma valproic acid levels were higher in the children rather than effect of age per se. The mechanism for this interaction is unknown but may involve inhibition of the carboxylesterases responsible for the metabolism of rufinamide [1].

Vigabatrin	Enhances the metabolism of rufinamide.
Consequence	Steady-state rufinamide levels can decrease by 14–30 %. This interaction is more substantial in children [1].
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

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Stiripentol

Stiripentol (Fig. 1) corresponds chemically to 4,4-dimethyl-1[3,4(methylenedioxy)-phenyl]-1-pentan-3-ol with an empirical formula of $C_{14}H_{18}O_3$ and a molecular weight of 234.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, stiripentol is rapidly absorbed ($T_{\max}=0.5\text{--}2\text{ h}$) with a bioavailability of $\geq 70\%$. Its volume of distribution is not known, and plasma protein binding is 99 %.

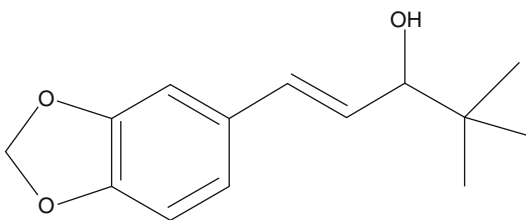


FIGURE 1 Stiripentol

Biotransformation

Stiripentol is extensively metabolized in the liver, primarily by demethylation and glucuronidation, to 13 different metabolites. The precise identification of the enzymes involved in metabolism is not known, but the principal enzymes are considered to be CYP1A2, CYP2C19, and CYP3A4.

Renal Excretion

Approximately 27 % of an administered dose is excreted as unchanged stiripentol in urine.

Elimination

Plasma elimination half-life values in adults are 4.5–13.0 h. Stiripentol elimination follows Michaelis-Menten (saturable, zero-order) kinetics so that plasma half-life and clearance is dose-dependent with values decreasing with increasing dose. As a result, steady-state plasma stiripentol levels increase more than proportionately after a dose increment.

Effects on Isoenzymes

At therapeutic concentrations, stiripentol in vitro substantially inhibits the activity of CYP2D6, CYP2C19, and CYP3A4. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and medicines can be expected.

No in vitro data on the induction potential of stiripentol on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

While the reference range for stiripentol in plasma is not well defined, concentrations of 4–22 mg/L (17–94 $\mu\text{mol/L}$) correlate with control of absence seizures in children, and in Dravet syndrome, concentrations of 8–12 mg/L (34–51 $\mu\text{mol/L}$) are reported to be effective. The conversion factor from mg/L to $\mu\text{mol/L}$ for stiripentol is 4.27 (i.e., 1 mg/L = 4.27 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Stiripentol affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of stiripentol – substantial.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine Consequence	Enhances the metabolism of stiripentol. Mean plasma clearance of stiripentol is increased by 300 % so that stiripentol plasma levels can decrease substantially. The interaction is probably the consequence of induction of CYP3A4 and CYP2C19 [1].
Clobazam Consequence	Inhibits the metabolism of stiripentol. Mean plasma stiripentol levels are increased by 25 % [2].

Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital	Enhances the metabolism of stiripentol. Mean plasma clearance of stiripentol is increased by 300 % so that stiripentol plasma levels can decrease substantially. The interaction is probably the consequence of induction of CYP3A4 and CYP2C19 [1].
Consequence	

Phenytoin Consequence	Enhances the metabolism of stiripentol. Mean plasma clearance of stiripentol is increased by 300 % so that stiripentol plasma levels can decrease substantially. The interaction is probably the consequence of induction of CYP3A4 and CYP2C19 [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone Consequence	Enhances the metabolism of stiripentol. Mean plasma clearance of stiripentol is increased by 300 % so that stiripentol plasma levels can decrease substantially. The interaction is probably the consequence of induction of CYP3A4 and CYP2C19 [1].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Valproic acid	Does not affect the pharmacokinetics of stiripentol [2].

Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

References

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Sulthiame

Sulthiame (Fig. 1) corresponds chemically to 4(1,1-diozothiazinan-2-yl)benzenesulfonamide with an empirical formula of $C_{10}H_{14}N_2O_4S_2$ and a molecular weight of 290.04.

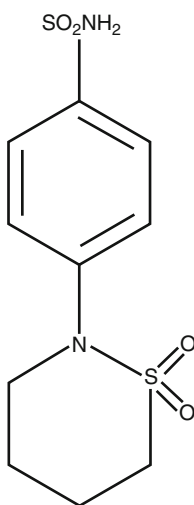


FIGURE 1 Sulthiame

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, stiripentol is rapidly absorbed ($T_{\max} = 1-5$ h) with a bioavailability of 100 %. Its volume of distribution is not known, and plasma protein binding is 29 %.

Biotransformation

Sulthiame undergoes moderate metabolism in the liver via unknown isoenzymes to unknown metabolites.

Renal Excretion

Approximately 32 % of an administered dose is excreted unchanged as sulthiame in urine.

Elimination

Plasma elimination half-life values in adults are 8–15 h, and in children, half-life values are 5–7 h.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of sulthiame on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in adult patients on polytherapy is most likely to occur at plasma sulthiame levels of 2–10 mg/L (7–34 $\mu\text{mol/L}$) while in children on polytherapy, it is most

likely to occur at plasma sulthiame levels of 1–3 mg/L (3–10 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for sulthiame is 3.45 (i.e., 1 mg/L = 3.45 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Sulthiame affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of sulthiame – minimal.

Interactions with AEDs

Acetazolamide	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p> <p>Acetazolamide and sulthiame are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].</p>
Carbamazepine	Enhances the metabolism of sulthiame.
Consequence	Plasma sulthiame levels can decrease [2].
Clobazam	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p>
Clonazepam	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p>

Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenobarbital	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenytoin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Primidone	Enhances the metabolism of sulthiame.
Consequence	Plasma sulthiame levels can decrease. A pharmacodynamic interaction has also been reported whereby the intensity of the side effects of sulthiame may increase, especially in children (e.g., dizziness, uncertain gait, and drowsiness) [3].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated. Topiramate and sulthiame are both weak inhibitors of carbonic anhydrase, and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].
Valproic acid	Does not affect the pharmacokinetics of sulthiame [2].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Zonisamide and sulthiame are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].

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Tiagabine

Tiagabine (Fig. 1) corresponds chemically to R-*n*-(4,4-di(3-methyl-thien-2-yl)-but-3-enyl)-nipecotic acid hydrochloride with an empirical formula of $C_{20}H_{25}NO_2S_2$ and a molecular weight of 375.5.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, tiagabine is rapidly absorbed (T_{\max} = 0.5–2 h) with a bioavailability of ≥ 90 %. Its volume of distribution is 1.0 L/kg, and plasma protein binding is 96 %.

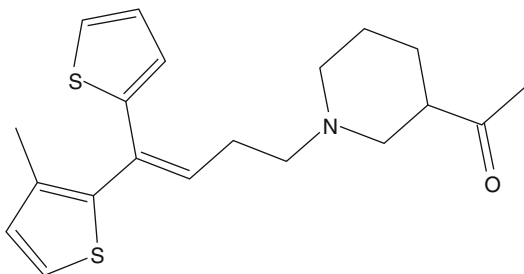


FIGURE 1 Tiagabine

Biotransformation

Tiagabine is substantially metabolized (98 %) in the liver, primarily by CYP3A4, to two 5-oxo-tiagabine isomers (E5 and Z-5; 60 %). The remaining 40 % of metabolites have yet to be identified.

Renal Excretion

Less than 2 % of an administered dose is excreted as unchanged tiagabine in urine.

Elimination

During tiagabine monotherapy, plasma elimination half-life values in adults are 5–9 h while during polytherapy with enzyme-inducing antiepileptic drugs, half-life values are 2–4 h.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of tiagabine on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on tiagabine monotherapy is most likely to occur at plasma tiagabine levels of 20–200 µg/L (53–532 nmol/L). The conversion factor from µg/L to nmol/L for tiagabine is 2.66 (i.e., 1 µg/L = 2.66 nmol/L).

Propensity to Be Associated with Pharmacokinetic Interactions

- Tiagabine affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of tiagabine – minimal.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine Consequence	Enhances the metabolism of tiagabine. Mean tiagabine plasma elimination half-life values in patients taking carbamazepine (plus other enzyme-inducing antiepileptic drugs) are 3.8–4.9 h compared to 5–8 h in healthy volunteers. Mean plasma tiagabine levels can be expected to be decreased by 40–70 %. The interaction is the consequence of induction of CYP3A4 [1].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Phenobarbital Consequence	Enhances the metabolism of tiagabine. Mean tiagabine plasma elimination half-life values in patients taking phenobarbital (plus other enzyme-inducing antiepileptic drugs) are 3.8–4.9 h compared to 5–8 h in healthy volunteers. Mean plasma tiagabine levels can be expected to be decreased by 40–70 %. The interaction is the consequence of induction of CYP3A4 [1].
Phenytoin Consequence	Enhances the metabolism of tiagabine. Mean tiagabine plasma elimination half-life values in patients taking phenytoin (plus other enzyme-inducing antiepileptic drugs) are 3.8–4.9 h compared to 5–8 h in healthy volunteers. Mean plasma tiagabine levels can be expected to be decreased by 40–70 %. The interaction is the consequence of induction of CYP3A4 [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin Consequence	Enhances the clearance of tiagabine. Enhances the clearance of tiagabine by 12 % and can decrease plasma tiagabine levels [2].
Primidone	Enhances the metabolism of tiagabine.

Consequence	Mean tiagabine plasma elimination half-life values in patients taking primidone (plus other enzyme-inducing antiepileptic drugs) are 3.8–4.9 h compared to 5–8 h in healthy volunteers. Mean plasma tiagabine levels can be expected to be decreased by 40–70 %. The interaction is the consequence of induction of CYP3A4 [1].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Valproic acid	Does not affect the pharmacokinetics of tiagabine [3].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated. Vigabatrin and tiagabine can have a synergistic anticonvulsant effect consequent to a pharmacodynamic interaction [4].
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Topiramate

Topiramate (Fig. 1) corresponds chemically to 2,3:4,5-bis-*O*-(1-methylethylidene)- β -D-fructopyranose sulfamate with an empirical formula of $C_{12}H_{21}NO_8S$ and a molecular weight of 339.37.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, topiramate is rapidly absorbed ($T_{\max} = 2\text{--}4\text{ h}$) with a bioavailability of $\geq 80\%$. Its volume of distribution is 0.6–0.8 L/kg, and plasma protein binding is 15 %.

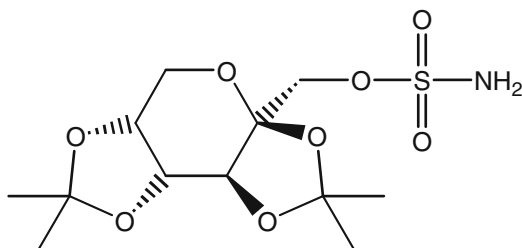


FIGURE 1 Topiramate

Biotransformation

Topiramate is not extensively metabolized in patients on monotherapy or in patients not prescribed with enzyme-inducing drugs, and typically, 40–50 % of a topiramate dose is excreted unchanged via the kidneys. However, in the presence of enzyme-inducing antiepileptic drugs, this value is doubled. Metabolites thus far identified include two hydroxy and two diol metabolites as well as several glucuronide conjugates, none of which constitutes more than 5 % of an administered dose. Although the specific CYP isoenzymes for the metabolism of topiramate have not been identified, it is evident that isoenzymes induced by carbamazepine and phenytoin play a major role.

Renal Excretion

Approximately 20–50 % of an administered dose is excreted as unchanged topiramate in urine.

Elimination

During monotherapy, plasma elimination half-life values in adults are 20–30 h while in polytherapy with enzyme-inducing antiepileptic drugs, half-life values are 10–15 h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Adults = 4–5 days later

Effects on Isoenzymes

At therapeutic concentrations, topiramate in vitro inhibits the activity of CYP2C19. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and other medicines can be expected.

Topiramate has no in vitro inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4.

No in vitro data on the induction potential of topiramate on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in adult patients on topiramate monotherapy is most likely to occur at plasma topiramate levels of 5–20 mg/L (15–59 $\mu\text{mol/L}$) while in children aged 6–12 years, it is most likely to occur at plasma topiramate levels of 2–21 mg/L (6–59 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for topiramate is 2.95 (i.e., 1 mg/L = 2.95 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Topiramate affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of topiramate – minimal.

Interactions with AEDs

Acetazolamide

The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Acetazolamide and topiramate are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they

	are administered together, an adverse pharmacodynamic interaction will occur [1].
Carbamazepine	Enhances the metabolism of topiramate.
Consequence	Plasma topiramate clearance is increased 2-fold so that mean plasma topiramate levels can be decreased by 40 % [2, 3].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	Enhances the clearance of topiramate.
Consequence	Plasma topiramate mean C_{\max} and AUC values are decrease by 8 and 18 %, respectively [4].
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically a pharmacokinetic interaction could occur.
Gabapentin	Does not affect the pharmacokinetics of topiramate [5].
Lacosamide	Does not affect the pharmacokinetics of topiramate [6].
Lamotrigine	Does not affect the pharmacokinetics of topiramate [7].
	Lamotrigine and topiramate can have a synergistic anticonvulsant effect consequent to a pharmacodynamic interaction [8].

Levetiracetam	Does not affect the pharmacokinetics of topiramate [9]. A pharmacodynamic interaction may occur whereby symptoms of decreased appetite, weight loss, and nervousness present [10].
Methsuximide	Enhances the metabolism of topiramate.
Consequence	Plasma topiramate levels can be decreased [5].
Oxcarbazepine	Enhances the metabolism of topiramate.
Consequence	Plasma topiramate levels can be decreased [5].
Phenobarbital	Enhances the metabolism of topiramate.
Consequence	Plasma topiramate clearance is increased 2-fold so that mean plasma topiramate levels can be decreased by 68 % [3, 11].
Phenytoin	Enhances the metabolism of topiramate.
Consequence	Plasma topiramate clearance is increased 2-fold so that mean plasma topiramate levels can be decreased by 50 % [3, 11].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	Does not affect the pharmacokinetics of topiramate [12].
Primidone	Enhances the metabolism of topiramate.
Consequence	Plasma topiramate clearance is increased 2-fold so that mean plasma topiramate levels can be decreased by 68 % [3, 11].

Retigabine	Does not affect the pharmacokinetics of topiramate [13].
Rufinamide	Does not affect the pharmacokinetics of topiramate [14].
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	Does not affect the pharmacokinetics of topiramate [5, 15]. Sulthiame and topiramate are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Valproic acid	Enhances the metabolism of topiramate.
Consequence	Mean plasma topiramate AUC values can be decreased by 14 % [16]. A pharmacodynamic interaction has been reported whereby topiramate induces a valproate-induced hyperammonemic encephalopathy in the context of normal liver function [17].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated. Zonisamide and topiramate are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi.

Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].

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Valproic Acid

Valproic acid (Fig. 1) corresponds chemically to *N*-dipropylacetic acid with an empirical formula of $C_8H_{16}O_2$ and a molecular weight of 144.21.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, valproic acid is rapidly absorbed (T_{max} is formulation-dependent) with a bioavailability of >90 %. Its volume of distribution in adults is 0.13–0.19 L/kg while in children, it is 0.20–0.30 L/kg, and plasma protein binding is 90 %.

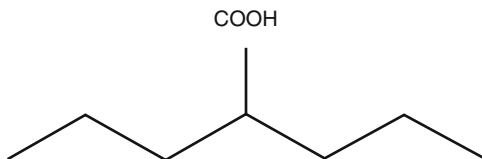


FIGURE 1 Valproic acid

Biotransformation

Valproic acid is extensively metabolized in the liver and involves multiple metabolic pathways including *O*-glucuronidation, β -oxidation, ω -oxidation hydroxylation, ketone formation, and desaturation. To date, in excess of 25 metabolites have been identified with valproic acid glucuronide and 3-oxo-valproic acid being by far the most abundant metabolites (~40 and 33 % of an administered dose, respectively). Hydroxylation to form 4-ene-valproic acid and other metabolites is via the action of CYP2A6, CYP2C9, CYP2C19, and CYP2B6 isoenzymes while *O*-glucuronidation is mediated by UGT1A3 and UGT2B7 isoenzymes.

Renal Excretion

Approximately 1–3 % of an administered dose is excreted as unchanged valproic acid in urine.

Elimination

In the absence of enzyme-inducing antiepileptic drugs, plasma elimination half-life values for adults are 12–16 h while in children, they are 8.6–12.3 h, and in infants, they are 8.4–12.5 h. In the presence of enzyme-inducing antiepileptic drugs, valproic acid half-life values for adults are 5–9 h while in children, half-life values are 7–9.4 h, and in infants, they are 4–8 h. Newborns eliminate valproic acid slowly with half-life values of 20–40 h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Adults = 2–4 days later

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of valproic acid on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on valproic acid monotherapy is most likely to occur at plasma valproic acid levels of 50–100 mg/L (350–700 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for valproic acid is 6.93 (i.e., 1 mg/L = 6.93 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Valproic acid affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of valproic acid – substantial.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Enhances the metabolism of valproic acid.
Consequence	<p>Mean plasma valproic acid levels can be decreased by 39 % [1].</p> <p>Coadministration with carbamazepine, and other enzyme-inducing antiepileptic drugs, does not only increase the clearance of valproic acid but may also change metabolic pathways. That patients treated with polytherapy have a greater incidence of valproic acid hepatotoxicity may be due to an increase in plasma levels of the 4-en and 2-4-en hepatotoxic metabolites [2].</p>

During combination therapy, carbamazepine may synergistically enhance the antiepileptic efficacy (partial seizures) of valproic acid. This effect may probably be the consequence of a pharmacodynamic interaction [3].

Clobazam	Inhibits the metabolism of valproic acid.
Consequence	Decreases the plasma clearance of valproic acid so that plasma valproic acid levels are increased [4].
Clonazepam	Does not affect the pharmacokinetics of valproic acid [5].
Eslicarbazepine acetate	Enhance the metabolism of valproic acid.
Consequence	Median plasma valproic acid levels are decreased by 12 % [6, 7].
Ethosuximide	Enhance the metabolism of valproic acid.
Consequence	Mean plasma valproic acid levels can be decreased by 28 % [8].
	During combination therapy, ethosuximide synergistically enhances the antiepileptic efficacy (absence seizures) and toxicity of valproic acid. These effects are probably the consequence of a pharmacodynamic interaction [9].
Felbamate	Inhibits the metabolism of valproic acid.
Consequence	Mean plasma valproic acid levels can be increased by 28–54 %. The interaction is the consequence of inhibition of β -oxidation [10].
Gabapentin	Does not affect the pharmacokinetics of valproic acid [11].
Lacosamide	Does not affect the pharmacokinetics of valproic acid [12, 13].
Lamotrigine	Enhance the metabolism of valproic acid.

Consequence	<p>Mean plasma valproic acid levels can be decreased by 25 %. The interaction is considered to be the consequence of induction of glucuronidation and β-oxidation [14].</p> <p>Concurrent valproic acid therapy is a risk factor for the development of skin rash with lamotrigine. The introduction of lamotrigine to patients already taking valproic acid should be undertaken with caution, using a low starting dose and a slow-dose escalation rate. However, there is no risk of rash if valproic acid is introduced to patients already stabilized on lamotrigine [15].</p> <p>During combination therapy, valproic acid synergistically enhances the antiepileptic efficacy (partial and generalized seizures) and toxicity of lamotrigine. This is considered to be the consequence of a pharmacodynamic interaction [16–18].</p>
Levetiracetam	Does not affect the pharmacokinetics of valproic acid [19].
Methsuximide	Enhance the metabolism of valproic acid.
Consequence	Plasma valproic acid levels can be decreased by 7–60 % [20].
Oxcarbazepine	Does not affect the pharmacokinetics of valproic acid [21].
Phenobarbital	Enhances the metabolism of valproic acid.
Consequence	<p>Mean plasma valproic acid levels can decrease by 37 %, and the mean plasma level to dose ratio for valproic acid can be decreased by 45 % [22].</p> <p>Coadministration with phenobarbital, and other enzyme-inducing</p>

antiepileptic drugs, does not only increase the clearance of valproic acid but may also change metabolic pathways. That patients treated with polytherapy have a greater incidence of valproic acid hepatotoxicity may be due to an increase in plasma levels of the 4-en and 2-4-en hepatotoxic metabolites [2].

Phenytoin

Enhances the metabolism of valproic acid.

Consequence

Mean plasma valproic acid levels can decrease by 37 %, and the mean plasma level to dose ratio for valproic acid can be decreased by 59 % [22].

Coadministration with phenytoin, and other enzyme-inducing antiepileptic drugs, does not only increase the clearance of valproic acid but may also change metabolic pathways. That patients treated with polytherapy have a greater incidence of valproic acid hepatotoxicity may be due to an increase in plasma levels of the 4-en and 2-4-en hepatotoxic metabolites [2, 22].

Piracetam

The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Pregabalin

Does not affect the pharmacokinetics of valproic acid [23].

Primidone

Enhances the metabolism of valproic acid.

Consequence

Mean plasma valproic acid levels can be decreased by 50 % [22].

Coadministration with primidone, and other enzyme-inducing antiepileptic drugs, does not only increase the

clearance of valproic acid but may also change metabolic pathways. That patients treated with polytherapy have a greater incidence of valproic acid hepatotoxicity may be due to an increase in plasma levels of the 4-en and 2-4-en hepatotoxic metabolites [2].

Retigabine Does not affect the pharmacokinetics of valproic acid [24].

Rufinamide Does not affect the pharmacokinetics of valproic acid [25].

Stiripentol Inhibits the metabolism of valproic acid.
Consequence Plasma valproic acid levels are increased. The interaction is considered to be the consequence of inhibition of CYP2C9 and CYP2C19 [2].

Sulthiame The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

Tiagabine Enhances the clearance of valproic acid.

Consequence Mean plasma valproic acid C_{max} and AUC values are decreased by 10 % and 12 % respectively via an unknown mechanism [26].

Topiramate Enhances the metabolism of valproic acid.

Consequence Mean plasma valproic acid AUC values can be decreased by 13 %. This is a consequence of the induction of β -oxidation (42 %) and ω -oxidation (36 %) and inhibition of the glucuronide conjugation pathway (35 %). The changes in metabolite production are noteworthy, particularly since the 4-ene metabolite has been implicated as a potential hepatotoxin [27].

	A pharmacodynamic interaction has been reported whereby topiramate induces a valproate-induced hyperammonemic encephalopathy in the context of normal liver function [28].
Vigabatrin	Does not affect the pharmacokinetics of valproic acid [29].
Zonisamide	Does not affect the pharmacokinetics of valproic acid [30].

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Vigabatrin

Vigabatrin (Fig. 1) corresponds chemically to (\pm)-amino-hex-5-enoic acid with an empirical formula of $C_6H_{11}NO_2$ and a molecular weight of 129.2.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, vigabatrin is rapidly absorbed ($T_{\max} = 1-2$ days) with a bioavailability of 60–80 %. Its volume of distribution in adults is 0.8 L/kg, and plasma protein binding is 0 %.

Biotransformation

Vigabatrin is not metabolized.

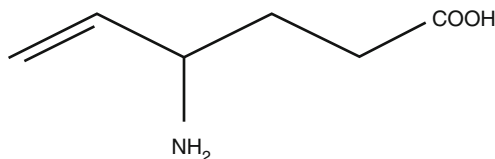


FIGURE 1 Vigabatrin

Renal Excretion

Approximately 100 % of an administered dose is excreted as unchanged vigabatrin in urine.

Elimination

Following a single dose, plasma elimination half-life values in adults are 5–8 h.

Effects on Isoenzymes

No in vitro data on the induction or inhibition potential of vigabatrin on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

At doses between 1,000 and 3,000 mg/day, the expected trough plasma vigabatrin levels are in the range of 0.8–36 mg/L (6–279 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for vigabatrin is 7.74 (i.e., 1 mg/L = 7.74 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Vigabatrin affects the pharmacokinetics of other drugs – does not interact.
- Other drugs affect the pharmacokinetics of vigabatrin – does not interact.

Interactions with AEDs

Acetazolamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Carbamazepine	Does not affect the pharmacokinetics of vigabatrin [1]. During combination therapy, carbamazepine may synergistically enhance the antiepileptic efficacy (partial seizures) of vigabatrin. This effect may probably be the consequence of a pharmacodynamic interaction [2].
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	Increases the excretion of vigabatrin.
Consequence	Mean plasma AUC values of the pharmacologically active S(+)-enantiomer is increased by 13 %, and urinary excretion is increased by a mean of 8 % [3].
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Lacosamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lamotrigine	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p> <p>Lamotrigine and vigabatrin in combination may be associated with substantial efficacy in patients with partial and secondary generalized tonic-clonic seizures consequent to a pharmacodynamic interaction [4].</p>
Levetiracetam	Does not affect the pharmacokinetics of vigabatrin [5].
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenobarbital	<p>Does not affect the pharmacokinetics of vigabatrin [1].</p> <p>During combination therapy for the treatment of infantile spasms, especially in patients with tuberous sclerosis, phenobarbital appears to delay or prevent the onset of seizure control by vigabatrin. This is considered to be the consequence of a pharmacodynamic interaction [6].</p>
Phenytoin	Does not affect the pharmacokinetics of vigabatrin [1].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Primidone	Does not affect the pharmacokinetics of vigabatrin [1].
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated. Tiagabine and vigabatrin can have a synergistic anticonvulsant effect consequent to a pharmacodynamic interaction [7].
Topiramate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Valproic acid	Does not affect the pharmacokinetics of vigabatrin [8].
Zonisamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Zonisamide

Zonisamide (Fig. 1) corresponds chemically to 1,2-benzisoxazole-3-methanesulfonamide with an empirical formula of $C_8H_8N_2O_3S$ and a molecular weight of 212.23.

Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, zonisamide is rapidly absorbed (T_{\max} = 2–5 days) with a bioavailability of >90 %. Its volume of distribution in adults is 1.0–1.9 L/kg, and plasma protein binding is 40 %.

Biotransformation

Zonisamide undergoes moderate metabolism in the liver, primarily acetylation to form *N*-acetyl zonisamide (20 %) and

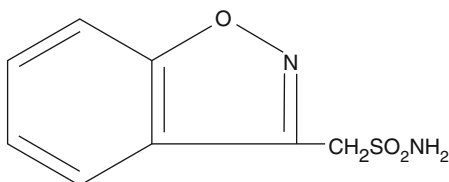


FIGURE 1 Zonisamide

reduction to form 2-sulfamoylacetylphenol (50 %), the latter being subsequently glucuronidated. The reduction of zonisamide to 2-sulfamoylacetylphenol is mediated by the CYP3A4 isoenzyme.

Renal Excretion

Approximately 30 % of an administered dose is excreted as unchanged zonisamide in urine.

Elimination

In the absence of enzyme-inducing antiepileptic drugs, plasma elimination half-life values in adults are 50–70 h while in the presence of enzyme-inducing antiepileptic drugs, half-life values are 25–35 h.

Effects on Isoenzymes

At therapeutic concentrations, zonisamide in vitro inhibits the activity of CYP2C19, CYP2C9, CYP2A6, and CYP2E1. Consequently, pharmacokinetic interactions of metabolic origin with other antiepileptic drugs and other medicines can be expected.

Zonisamide has no in vitro inhibitory effect on the activity of CYP1A2, CYP2D6, and CYP3A4.

No in vitro data on the induction potential of zonisamide on human CYP or UGT isoenzymes have been published.

Therapeutic Drug Monitoring

Optimum seizure control in patients on zonisamide monotherapy is most likely to occur at plasma zonisamide levels of 10–40 mg/L (47–188 $\mu\text{mol/L}$). The conversion factor from mg/L to $\mu\text{mol/L}$ for zonisamide is 4.71 (i.e., 1 mg/L = 4.71 $\mu\text{mol/L}$).

Propensity to Be Associated with Pharmacokinetic Interactions

- Zonisamide affects the pharmacokinetics of other drugs – minimal.
- Other drugs affect the pharmacokinetics of zonisamide – minimal.

Interactions with AEDs

Acetazolamide	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p> <p>Acetazolamide and zonisamide are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].</p>
Carbamazepine	Enhances the metabolism of zonisamide.
Consequence	<p>Plasma zonisamide half-life values can be decreased to ~36 h compared to 60 h observed in untreated volunteers.</p> <p>Concurrent oral clearance values are increased to 0.98 L/h from 0.7 L/h. The interaction is the consequence of induction of zonisamide metabolism through CYP3A4 [2].</p>
Clobazam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Clonazepam	Does not affect the pharmacokinetics of zonisamide [3].

Eslicarbazepine acetate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Ethosuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Felbamate	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Gabapentin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Lacosamide	Does not affect the pharmacokinetics of zonisamide [4].
Lamotrigine	Does not affect the pharmacokinetics of zonisamide [5].
Levetiracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Methsuximide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Oxcarbazepine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Phenobarbital	Enhances the metabolism of zonisamide.
Consequence	Plasma zonisamide half-life values can be decreased to ~38 h compared to 60 h observed in untreated volunteers. Concurrent clearance values are increased by 27%. The interaction is the consequence of induction of zonisamide metabolism through CYP3A4 [6].
Phenytoin	Enhances the metabolism of zonisamide.
Consequence	Plasma zonisamide half-life values can be decreased to ~28 h compared to 60 h observed in untreated volunteers.

	Concurrent oral clearance values are increased to 1.29 L/h from 0.7 L/h. The interaction is the consequence of induction of zonisamide metabolism through CYP3A4 [7].
Piracetam	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Pregabalin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Primidone	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Consequence	As primidone is metabolized to phenobarbital, the same interaction as that described for phenobarbital can be expected.
Retigabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Rufinamide	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Stiripentol	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.
Sulthiame	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

Sulthiame and zonisamide are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].

Tiagabine	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
Topiramate	<p>The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.</p> <p>Topiramate and zonisamide are both weak inhibitors of carbonic anhydrase and, as a direct result, may independently increase the risk of renal calculi. Consequently, there is a theoretical potential that when they are administered together, an adverse pharmacodynamic interaction will occur [1].</p>
Valproic acid	Does not affect the pharmacokinetics of zonisamide [8].
Vigabatrin	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

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Part II
Drug Interactions Between
AEDs and Non-AED Drugs:
Interactions Affecting AEDs

Acetazolamide

There have been no reports of the effect of non-AED drugs on the pharmacokinetics or pharmacodynamics of acetazolamide.

Carbamazepine

Analgesics

Aspirin

Salicylic acid does not affect the pharmacokinetics of carbamazepine [1].

Propoxyphene (dextropropoxyphene)

Propoxyphene inhibits the metabolism of carbamazepine, probably via an action on CYP3A4. Typically, mean plasma carbamazepine levels can increase by 24–64 % but occasionally larger increases can occur (800 %). Concurrent mean plasma carbamazepine-10,11-epoxide levels can be decreased by 42 % [2–4].

Paracetamol

Paracetamol does not affect the pharmacokinetics of carbamazepine [1].

Phenylbutazone

Phenylbutazone does not affect the pharmacokinetics of carbamazepine [1].

Tolfenamic acid

Tolfenamic acid does not affect the pharmacokinetics of carbamazepine [1].

Antibacterials

<i>Azithromycin</i>	Azithromycin does not affect the pharmacokinetics of carbamazepine [5].
<i>Ciprofloxacin</i>	Ciprofloxacin can increase plasma carbamazepine levels [6].
<i>Clarithromycin</i>	Clarithromycin inhibits the metabolism of carbamazepine, probably via an action on CYP3A4, and can increase mean plasma carbamazepine levels by 100 %. Plasma carbamazepine-10,11-epoxide levels have been reported either to be unaffected or to decrease [7, 8].
<i>Dirithromycin</i>	Dirithromycin does not affect the pharmacokinetics of carbamazepine [9].
<i>Erythromycin</i>	Erythromycin inhibits the metabolism of carbamazepine, probably via an action on CYP3A4, and can increase plasma carbamazepine levels 2–4-fold. Plasma carbamazepine-10,11-epoxide levels can be concurrently decreased by 41 % [10].
<i>Flurithromycin</i>	Flurithromycin inhibits the metabolism of carbamazepine, probably via an action on CYP3A4, and can increase mean plasma carbamazepine AUC values by 18 %. Mean plasma carbamazepine-10,11-epoxide levels can be concurrently decreased by 23 % [11].
<i>Isotretinoin</i>	Isotretinoin can increase plasma carbamazepine AUC values by 11–24 % and can decrease plasma carbamazepine-10,11-epoxide AUC values by 21–24 % [12].
<i>Josamycin</i>	Josamycin inhibits the metabolism of carbamazepine, probably via an action on CYP3A4, and can increase mean

<i>Metronidazole</i>	plasma carbamazepine AUC values by 18 %. Plasma carbamazepine-10,11-epoxide levels are unaffected [13]. Metronidazole can increase plasma carbamazepine levels by ~ 60 %. The mechanism of this interaction is not known. [14]
<i>Ponsinomycin (miocamycin)</i>	Ponsinomycin inhibits the metabolism of carbamazepine, probably via an action on CYP3A4, and can increase mean plasma carbamazepine AUC values by 13 % and decrease mean plasma carbamazepine-10,11-epoxide levels by 26 % [15].
<i>Roxithromycin</i>	Roxithromycin does not affect the pharmacokinetics of carbamazepine [16].
<i>Troleandomycin</i>	Troleandomycin inhibits the metabolism of carbamazepine, probably via an action on CYP3A4, and can increase plasma carbamazepine levels 2–3-fold [17].

Antifungal Agents

<i>Fluconazole</i>	Fluconazole inhibits the metabolism of carbamazepine, probably by inhibiting CYP3A4, and can increase plasma carbamazepine levels by 147 % [18].
<i>Ketoconazole</i>	Ketoconazole inhibits the metabolism of carbamazepine and can increase mean plasma carbamazepine levels by 29 %. Plasma carbamazepine-10,11-epoxide levels are not affected. The mechanism is considered to be via an action on CYP3A4 [19].

Miconazole Miconazole inhibits the metabolism of carbamazepine and can increase plasma carbamazepine levels [20].

Antineoplastic Agents

Cisplatin Cisplatin may decrease plasma carbamazepine levels by decreasing cisplatin absorption [21].

Tamoxifen Tamoxifen does not affect the pharmacokinetics of carbamazepine [22].

Antituberculous Agents

Isoniazid Isoniazid inhibits the metabolism of carbamazepine and can result in a 45 % decrease in clearance and an increase in plasma carbamazepine levels of up to 85 % [23, 24].

Rifampicin Rifampicin enhances the metabolism of carbamazepine and can decrease plasma carbamazepine levels [25].

Antiulcer Drugs

Histamine H₂-Receptor Antagonists

Cimetidine Cimetidine inhibits the metabolism of carbamazepine, via an action on CYP3A4, and can increase plasma carbamazepine levels by 17 %. In many patients this interaction does not occur or is transient [26, 27].

Ranitidine Ranitidine does not affect the pharmacokinetics of carbamazepine [28].

Proton Pump Inhibitors

Omeprazole Conflicting effects have been reported. A single-dose carbamazepine study of patients found an increase in mean plasma carbamazepine AUC values of 75 %, a decrease in mean plasma carbamazepine clearance values of 40 %, and an increase in mean plasma carbamazepine half-life values of 118 %. However, another patient study whereby carbamazepine treatment was long-term found a small nonsignificant decrease in carbamazepine plasma levels [29, 30].

Pantoprazole Pantoprazole does not affect the pharmacokinetics of carbamazepine [31].

Antiviral Agents

Efavirenz Efavirenz enhances the metabolism of carbamazepine, via an action on CYP3A4, and can decrease mean plasma carbamazepine C_{max} values by 29 % and mean plasma carbamazepine AUC values by 27 %. Plasma carbamazepine-10,11-epoxide levels are not affected [32].

***Lopinavir/
ritonavir*** Lopinavir combined with ritonavir can inhibit the metabolism of carbamazepine, via an action on CYP3A4, and can increase plasma carbamazepine levels by 46 % [33].

<i>Nelfinavir</i>	Nelfinavir inhibits the metabolism of carbamazepine, via an action on CYP3A4, and can increase plasma carbamazepine levels by 53 % [33].
<i>Ritonavir</i>	Ritonavir inhibits the metabolism of carbamazepine, via an action on CYP3A4, and can increase plasma carbamazepine levels by 180 % [34].

Cardiovascular Drugs

Antiarrhythmics

<i>Amiodarone</i>	Amiodarone does not affect the pharmacokinetics of carbamazepine [35].
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Antihypertensive Agents

<i>Diltiazem</i>	Diltiazem inhibits the metabolism of carbamazepine and can increase plasma carbamazepine levels by 55–100 % [36].
<i>Nifedipine</i>	Nifedipine does not affect the pharmacokinetics of carbamazepine [37].
<i>Verapamil</i>	Verapamil inhibits the metabolism of carbamazepine and can increase mean plasma carbamazepine levels by 46 %. Plasma carbamazepine-10,11-epoxide levels are unaffected [38].

Antiplatelet Drugs

<i>Ticlopidine</i>	Ticlopidine inhibits the metabolism of carbamazepine, perhaps via an action
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on CYP3A4, and can increase plasma carbamazepine levels by up to 74 % [39].

Lipid-Lowering Drugs

<i>Cholestyramine</i>	Cholestyramine does not affect the pharmacokinetics of carbamazepine [40].
<i>Colestipol</i>	Colestipol can reduce the absorption of carbamazepine by 10 % [40].
<i>Gemfibrozil</i>	Plasma carbamazepine levels can be increased by 30–65 %. The suggested mechanism is that the clearance of carbamazepine is increased in those patients with elevated cholesterol and total lipids, thus when the condition is treated with gemfibrozil, clearance becomes more normal resulting in an increase in plasma carbamazepine levels [41].

Oral Anticoagulants

<i>Pentoxifylline</i>	Pentoxifylline does not affect the pharmacokinetics of carbamazepine [42].
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Herbal Remedies

<i>Grapefruit juice (furanocoumarins)</i>	Grzpefruit juice inhibits the metabolism of carbamazepine, via an action on CYP3A4, and can increase mean carbamazepine levels by 39 % [43].
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***St John's Wort
(Hypericum
perforatum)***

St John's Wort enhances the metabolism of carbamazepine by inducing CYP3A4 and possibly by affecting the activity of drug transporters in the gastrointestinal tract. Indeed, St John's Wort has been shown to decrease plasma carbamazepine levels after a single dose of carbamazepine, although no interaction was identified at steady state [44].

Psychotropic Drugs

Antidepressants

Amoxapine

Amoxapine does not affect plasma carbamazepine levels. However, plasma carbamazepine-10,11-epoxide levels can be increased [45].

Citalopram

Citalopram does not affect the pharmacokinetics of carbamazepine [46].

Fluoxetine

Fluoxetine inhibits the metabolism of carbamazepine.

Mean plasma carbamazepine AUC values are increased by 27 %, while mean plasma AUC values of its pharmacologically active metabolite, carbamazepine-10,11-epoxide, are increased by 31 %. However, the interaction appears to be variable with some studies reporting no effect [47, 48].

Fluvoxamine

Conflicting effects have been reported.

The interaction appears to be variable with plasma levels of carbam-

	azepine and its metabolite, carbamazepine-10,11-epoxide, ranging from no effect to a 71 % increase in levels [48, 49].
<i>Nefazodone</i>	Nefazodone inhibits the metabolism of carbamazepine. Plasma carbamazepine levels are increased by up to 3-fold [50–52].
<i>Paroxetine</i>	Paroxetine does not affect the pharmacokinetics of carbamazepine [53].
<i>Sertraline</i>	Sertraline does not affect the pharmacokinetics of carbamazepine [54].
<i>Trazodone</i>	Trazodone inhibits the metabolism of carbamazepine and can increase plasma carbamazepine levels by 26 % [55].
<i>Venlafaxine</i>	Venlafaxine does not affect the pharmacokinetics of carbamazepine [56].
<i>Viloxazine</i>	Viloxazine inhibits the metabolism of carbamazepine and can increase mean plasma carbamazepine levels by 55 % and mean plasma carbamazepine-10,11-epoxide levels by 16 % [57].

Antipsychotics

<i>Haloperidol</i>	Haloperidol inhibits the metabolism of carbamazepine and can increase plasma carbamazepine levels by 40 % [58].
<i>Loxapine</i>	Loxapine does not affect plasma carbamazepine levels. However, plasma carbamazepine-10,11-epoxide levels can be increased [45].
<i>Quetiapine</i>	Quetiapine increases plasma carbamazepine-10,11-epoxide levels so that the

	plasma carbamazepine-10,11-epoxide/ carbamazepine ratio is increased by 3–4-fold [59].
<i>Risperidone</i>	Risperidone inhibits the metabolism of carbamazepine and can increase mean plasma carbamazepine levels, probably via inhibition of CYP3A4, by 19 % [60].
<i>Thioridazine</i>	Thioridazine does not affect the pharmacokinetics of carbamazepine [61].

Steroids

<i>Danazol</i>	Danazol inhibits the metabolism of carbamazepine and can increase plasma carbamazepine levels by 38–123 % [62].
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Miscellanea

<i>Disulfiram</i>	Disulfiram does not affect the pharma- cokinetics of carbamazepine [63].
<i>Influenza vaccination</i>	Influenza vaccination can increase plasma carbamazepine levels [64].
<i>Nicotinamide</i>	Nicotinamide inhibits the metabolism of carbamazepine and can decrease carbamazepine clearance by 58–81 % and increases plasma carbamazepine levels [65].
<i>Orlistat</i>	Orlistat does not affect the pharmaco- kinetics of carbamazepine [66].
<i>Oxiracetam</i>	Oxiracetam does not affect the pharma- cokinetics of carbamazepine [67].
<i>Probenecid</i>	Probenecid enhances the metabolism of carbamazepine, via an action on CYP3A4 and CYP2C8, and can

	decrease mean carbamazepine AUC values by 19 % and can increase mean carbamazepine-epoxide AUC values by 33 % [68].
<i>Terfenadine</i>	Terfenadine displaces carbamazepine from its plasma protein binding sites and can increase free carbamazepine plasma levels resulting in carbamazepine toxicity [69].
<i>Theophylline</i>	Theophylline enhances the metabolism of carbamazepine and can decrease mean plasma carbamazepine AUC values by 29 % [70].

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Clobazam

Cimetidine

The effect of cimetidine on the pharmacokinetics of clobazam is conflicting.

Cimetidine can increase mean plasma clobazam AUC values by 17 % and increase mean half-life values by 11 % without affecting the pharmacokinetics of *N*-desmethyclobazam (the pharmacologically active metabolite of clobazam). Also, cimetidine has been reported to increase mean plasma clobazam AUC values by 59 % and increase mean plasma half-life values by 40 % along with a concurrent increase in mean *N*-desmethyclobazam AUC and half-life values of 57 and 90 %, respectively [1,2].

Etravirine

Etravirine inhibits the metabolism of clobazam and can increase plasma clobazam and plasma *N*-desmethyclobazam levels [3].

Ketoconazole

Ketoconazole inhibits the metabolism of clobazam and can increase mean plasma clobazam and *N*-desmethyclobazam AUC values by 54 and 18 %, respectively [4].

<i>Miconazole</i>	Miconazole inhibits the metabolism of clobazam and its pharmacologically active metabolite <i>N</i> -desmethyloclobazam and can increase plasma clobazam levels by 85 % and plasma <i>N</i> -desmethyloclobazam levels by 6.5-fold [5].
<i>Omeprazole</i>	Omeprazole inhibits the metabolism of clobazam and can increase mean plasma clobazam and <i>N</i> -desmethyloclobazam AUC values by 30 and 36 %, respectively [4].
<i>Oxiracetam</i>	Oxiracetam does not affect the pharmacokinetics of clobazam [6].

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Clonazepam

<i>Amiodarone</i>	Clonazepam toxicity was observed in a patient co-prescribed amiodarone, which resolved upon clonazepam withdrawal [1].
<i>Fluoxetine</i>	Fluoxetine does not affect the pharmacokinetics of clonazepam [2].
<i>Sertraline</i>	Sertraline does not affect the pharmacokinetics of clonazepam [3].

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Eslicarbazepine Acetate

There have been no reports of the effect of non-AED drugs on the pharmacokinetics or pharmacodynamics of eslicarbazepine acetate.

Ethosuximide

Isoniazid

Isoniazid inhibits the metabolism of ethosuximide and can increase plasma ethosuximide levels by 42 % [1].

Rifampicin

Rifampicin enhances the metabolism of ethosuximide and can decrease plasma ethosuximide levels [2].

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Felbamate

<i>Antacids</i>	Concurrent administration of antacids (Maalox Plus; aluminum/magnesium hydroxides) does not affect the rate or extent of felbamate absorption [1].
<i>Erythromycin</i>	Erythromycin does not affect the pharmacokinetics of felbamate [2].

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Gabapentin

<i>Antacids</i>	Antacids (Maalox aluminumhydroxide/magnesium hydroxide) can reduce the oral bioavailability of gabapentin by 20 %. To avoid problems, administration of gabapentin and antacids should be separated by at least 2 h [1].
<i>Hydrocodone</i>	Hydrocodone can increase gabapentin absorption and increase plasma gabapentin levels [2].
<i>Cimetidine</i>	Cimetidine can increase mean plasma gabapentin AUC values by 24 % [3].
<i>Morphine</i>	Morphine can increase gabapentin absorption and increase plasma gabapentin levels [2].
<i>Naproxen</i>	Naproxen can increase gabapentin absorption and increase mean plasma gabapentin AUC values by 13 % [3].
<i>Probenecid</i>	Probenecid does not affect the pharmacokinetics of gabapentin [4].

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Lacosamide

<i>Digoxin</i>	Digoxin does not affect the pharmacokinetics of lacosamide [1].
<i>Metformin</i>	Metformin does not affect the pharmacokinetics of lacosamide [1].
<i>Omeprazole</i>	Omeprazole does not affect the pharmacokinetics of lacosamide [2].
<i>Oral contraceptives</i>	Oral contraceptives do not affect the pharmacokinetics of lacosamide [1].

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Lamotrigine

Analgesics

Acetaminophen Acetaminophen can decrease mean plasma lamotrigine AUC values by 20 % and mean elimination half-life values by 15 % and enhances the urinary elimination of lamotrigine via an unknown mechanism [1].

Antimicrobials

Antituberculous Agents

Ethambutol Ethambutol enhances the metabolism of lamotrigine and can increase plasma lamotrigine clearance 3-fold [2].

Isoniazid Isoniazid inhibits the metabolism of lamotrigine and can decrease plasma lamotrigine clearance by 15 % [2].

Rifampicin Rifampicin enhances the metabolism of lamotrigine, via an action on glucuronidation, and can decrease mean plasma lamotrigine AUC values by 44 % [3].

Antifungal Agents

Fluconazole Fluconazole does not affect the pharmacokinetics of lamotrigine [4].

Antiviral Agents

Atazanavir Atazanavir can enhance the metabolism of lamotrigine, via an action on UGT1A4, and can decrease mean plasma lamotrigine AUC values by 12 % and mean plasma half-life values by 9 % [5].

**Atazanavir/
ritonavir** Atazanavir in combination with ritonavir can enhance the metabolism of lamotrigine, via an action on UGT1A4, and can decrease mean plasma lamotrigine AUC values by 32 % and mean plasma half-life values by 27 % [5].

**Lopinavir/
ritonavir** Lopinavir combined with low dose ritonavir can enhance the metabolism of lamotrigine, via an action on UGT1A4, and can decrease mean plasma lamotrigine levels by 55 % [6].

Raltegravir Raltegravir does not affect the pharmacokinetics of lamotrigine [7].

Ritonavir Ritonavir can enhance the metabolism of lamotrigine, via induction of UDP-glucuronyltransferases, and can decrease plasma lamotrigine levels [5].

Antiulcer Drugs

Histamine H₂-Receptor Antagonists

Cimetidine Cimetidine does not affect the pharmacokinetics of lamotrigine [3].

Psychotropic Drugs

Antidepressants

Paroxetine Paroxetine does not affect the pharmacokinetics of lamotrigine [8].

Sertraline Sertraline can increase plasma lamotrigine levels 2-fold. Inhibition of lamotrigine glucuronidation by sertraline has been proposed to explain this interaction [9].

Antipsychotics

Aripiprazole Aripiprazole can decrease mean plasma lamotrigine C_{max} and AUC values by 12 and 9 %, respectively [10].

Clozapine Clozapine does not affect the pharmacokinetics of lamotrigine [11].

Risperidone Risperidone does not affect the pharmacokinetics of lamotrigine [11].

Olanzapine Olanzapine can decrease mean plasma lamotrigine C_{max} and AUC values by 20 and 24 %, respectively. Induction of lamotrigine glucuronidation by olanzapine has been proposed to explain this interaction [12].

Steroids

Oral contraceptives Oral contraceptives enhance the metabolism of lamotrigine and can decrease plasma lamotrigine levels by 40–65 % [13].

Miscellanea

Bupropion Bupropion does not affect the pharmacokinetics of lamotrigine [14].

Orlistat Orlistat can decrease plasma lamotrigine levels by reducing lamotrigine gastrointestinal absorption [15].

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Levetiracetam

<i>Antacids</i>	Calcium carbonate and aluminum hydroxide do not affect the pharmacokinetics of levetiracetam [1].
<i>Digoxin</i>	Digoxin does not affect the pharmacokinetics of levetiracetam [2].
<i>Meropenem</i>	Meropenem does not affect the pharmacokinetics of levetiracetam [3].
<i>Probenecid</i>	Probenecid does not affect the pharmacokinetics of levetiracetam. However, the plasma level of its primary nonpharmacologically active metabolite, ucbLO59, increases 2.5-fold consequent to a 61 % decrease in tubular excretion [4].
<i>Oral contraceptives</i>	Oral contraceptives do not affect the pharmacokinetics of levetiracetam [5].
<i>Warfarin</i>	Warfarin does not affect the pharmacokinetics of levetiracetam [6].

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Methsuximide

There have been no reports of the effect of non-AED drugs on the pharmacokinetics or pharmacodynamics of methsuximide.

Oxcarbazepine

<i>Cimetidine</i>	Cimetidine does not affect the pharmacokinetics of oxcarbazepine [1].
<i>Erythromycin</i>	Erythromycin does not affect the pharmacokinetics of oxcarbazepine [2].
<i>Propoxyphene (dextropropoxyphene)</i>	Propoxyphene does not affect the pharmacokinetics of oxcarbazepine [3].
<i>Temozolomide</i>	Temozolomide does not affect the pharmacokinetics of oxcarbazepine [4].
<i>Verapamil</i>	Verapamil can decrease mean plasma 10-hydroxycarbazepine AUC values by 20 % [5].
<i>Viloxazine</i>	Viloxazine can increase mean plasma 10-hydroxycarbazepine levels by 11 % [6].

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Phenobarbital

BCNU (13-bis (2-chloroethyl)- 1-nitrosourea)	BCNU does not affect the pharmacokinetics of phenobarbital [1].
Bleomycin	Bleomycin does not affect the pharmacokinetics of phenobarbital [2].
Chloramphenicol	Chloramphenicol inhibits the metabolism of phenobarbital and can increase plasma phenobarbital levels [3].
Cisplatin	Cisplatin does not affect the pharmacokinetics of phenobarbital [1].
Dicoumarol	Dicoumarol can decrease plasma phenobarbital levels [4].
Disulfiram	Disulfiram does not affect the pharmacokinetics of phenobarbital [5].
Pindolol	Pindolol does not affect the pharmacokinetics of phenobarbital [6].
Propoxyphene (dextropro- poxyphe)	Propoxyphene can increase plasma phenobarbital levels by 20 % [7].

Teniposide	Teniposide does not affect the pharmacokinetics of phenobarbital [8].
Thioridazine	Thioridazine can decrease plasma phenobarbital levels [9].
Tipranavir/ ritonavir	Tipranavir combined with ritonavir can enhance the metabolism of phenobarbital and can decrease phenobarbital levels by 50 % [10].
Troleandomycin	Troleandomycin can decrease plasma phenobarbital levels by 23 % [11].
Vinblastine	Vinblastine does not affect the pharmacokinetics of phenobarbital [12].

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Phenytoin

Analgesics

Aspirin

Salicylic acid does not affect the pharmacokinetics of phenytoin [1].

Propoxyphene (dextropropoxyphene)

Propoxyphene can increase plasma phenytoin levels. This interaction is consistent with in vitro and clinical reports of inhibition of other CYP2C9 substrates by propoxyphene [2].

Fenylramidol

Fenylramidol inhibits the metabolism of phenytoin and can increase plasma phenytoin levels [3].

Ibuprofen

Ibuprofen does not affect the pharmacokinetics of phenytoin [4].

Paracetamol

Paracetamol does not affect the pharmacokinetics of phenytoin [1].

Phenylbutazone

The interaction between phenylbutazone and phenytoin is complex in that initially plasma phenytoin levels can decrease (~20 %) and then they increase. The mechanism of this interaction involves a concurrent plasma

Tolfenamic acid protein binding displacement interaction and an inhibition of phenytoin metabolism by phenylbutazone [1]. Tolfenamic acid does not affect the pharmacokinetics of phenytoin [1].

Antibacterials

Amoxicillin Amoxicillin does not affect the pharmacokinetics of phenytoin [5].

Chloramphenicol Chloramphenicol inhibits the metabolism of phenytoin and can increase plasma phenytoin levels by 177 % [6].

Ciprofloxacin Ciprofloxacin can decrease plasma phenytoin levels by 80 % [7].

There have been conflicting data on a possible interaction of ciprofloxacin with phenytoin, with no change, a decrease or an increase in plasma phenytoin level having all been reported [8].

Clarithromycin Clarithromycin can increase mean plasma phenytoin levels by 82 % [9].

Clinafloxacin Clinafloxacin can decrease mean clearance values by 15 % and increase mean plasma phenytoin AUC values by 20 % [10].

Co-trimoxazole Co-trimoxazole (a mixture of sulfamethoxazole and trimethoprim) inhibits the metabolism of phenytoin and can increase plasma phenytoin levels [5].

Erythromycin Erythromycin does not affect the pharmacokinetics of phenytoin [11].

Isotretinoin Isotretinoin does not affect the pharmacokinetics of phenytoin [12].

Metronidazole There have been conflicting data on a possible interaction of metronidazole

- with phenytoin, with no change or an inhibition of phenytoin metabolism and a decrease in phenytoin clearance by 15 % resulting in an increase in plasma phenytoin levels [13, 14].
- Sulfadiazine*** Sulfadiazine inhibits the metabolism of phenytoin and can decrease mean plasma phenytoin clearance values by 45 % and increase mean plasma phenytoin half-life values by 80 % [15].
- Sulfadimethoxine*** Sulfadimethoxine does not affect the pharmacokinetics of phenytoin [15].
- Sulfaphenazole*** Sulfaphenazole inhibits the metabolism of phenytoin and can decrease mean plasma phenytoin clearance values by 67 % and increase mean plasma phenytoin half-life values by 237 % [15].
- Sulfamethizole*** Sulfamethizole inhibits the metabolism of phenytoin and can decrease mean plasma phenytoin clearance values by 36 % and increase mean plasma phenytoin half-life values by 66 % [15].
- Sulfamethoxazole*** Sulfamethoxazole inhibits the metabolism of phenytoin and can increase mean plasma phenytoin half-life values but does not affect mean plasma phenytoin clearance values [15].
- Sulfamethoxazole/trimethoprim*** Sulfamethoxazole/trimethoprim in combination inhibits the metabolism of phenytoin and can decrease mean plasma phenytoin clearance values by 27 % and increase mean plasma phenytoin half-life values by 39 % [15].

Sulfamethoxydiazine***Sulfamethoxypyridazine******Trimethoprim***

Sulfamethoxydiazine does not affect the pharmacokinetics of phenytoin [15]. Sulfamethoxypyridazine does not affect the pharmacokinetics of phenytoin [15]. Trimethoprim inhibits the metabolism of phenytoin and can increase mean phenytoin half-life values by 51 % and decrease mean clearance values by 30 % [15].

Some of these sulfonamides concurrently displace phenytoin from plasma protein binding sites (primarily albumin), and therefore measurement of total phenytoin level may underestimate the increase in the level of the free, pharmacologically active drug. In this setting, patient management may benefit from monitoring free phenytoin levels [15].

Antifungal Agents

Fluconazole

Fluconazole inhibits phenytoin metabolism, via an action on CYP2C9 and CYP2C19, and can increase mean plasma phenytoin levels by 128 % [16].

Itraconazole

Itraconazole can increase mean plasma phenytoin AUC values by 10 % [17].

Ketoconazole

Ketoconazole does not affect the pharmacokinetics of phenytoin [18].

Miconazole

Miconazole can increase plasma phenytoin levels by 50–181 % [19].

Posaconazole

Posaconazole inhibits phenytoin metabolism and can increase mean plasma phenytoin AUC values by 25 % [20].

Voriconazole Voriconazole inhibits the metabolism of phenytoin, via an action on CYP2C9 and CYP2C19, and can increase mean plasma phenytoin AUC values by 80 % and mean plasma phenytoin levels by 70 % [21].

Antineoplastic Agents

BCNU
(13-bis
(2-chloroethyl)-
1-nitrosourea) BCNU does not affect the pharmacokinetics of phenytoin [22].

Bleomycin Bleomycin can significantly decrease plasma phenytoin levels, but this may be a consequence of antineoplastic damage to the intestinal mucosa and impaired phenytoin absorption. Only a mean 32 % of a phenytoin dose is absorbed during combination therapy with cisplatin, vinblastine, and bleomycin [23].

Capecitabine Capecitabine can increase plasma phenytoin levels [24].

Carboplatin Carboplatin can decrease plasma phenytoin levels by 50 %. This interaction may be the consequence of enhanced hepatic metabolism or a displacement of phenytoin from its plasma protein binding sites [25].

Cisplatin Cisplatin can decrease plasma phenytoin levels by up to 78 %. Cisplatin possibly enhances the metabolism of phenytoin although a change in volume of distribution could also be responsible for this interaction [22].

<i>Doxifluridine</i>	Doxifluridine inhibits the metabolism of phenytoin, probably via an action on CYP2C9, and can increase plasma phenytoin levels 4-fold [26].
<i>5-Fluorouracil</i>	5-Fluorouracil inhibits the metabolism of phenytoin, via an action on CYP2C9, and can increase plasma phenytoin levels [27].
<i>Methotrexate</i>	Methotrexate can decrease plasma phenytoin levels, but this may be a consequence of antineoplastic damage to the intestinal mucosa and impaired phenytoin absorption [28].
<i>POMP-24</i>	POMP-24 (a mixture of prednisone, vincristine, methotrexate, and 6-mercaptopurine) enhances the metabolism of phenytoin and can decrease plasma phenytoin levels by 72 % [29].
<i>Tamoxifen</i>	Tamoxifen inhibits the metabolism of phenytoin, via an action on CYP2C9, and can increase plasma phenytoin levels by 44 % [30].
<i>Teniposide</i>	Teniposide does not affect the pharmacokinetics of phenytoin [31].
<i>UFT</i>	UFT (a mixture of uracil and the 5-fluorouracil prodrug tegafur) inhibits the metabolism of phenytoin and can increase plasma phenytoin levels [32].
<i>Vinblastine</i>	Vinblastine can decrease plasma phenytoin levels by 39 %. This interaction may be a consequence of antineoplastic damage to the intestinal mucosa and impaired phenytoin absorption [28]. During combination treatment with cisplatin, vinblastine, and bleomycin, as little as a mean 32 % of a phenytoin dose is absorbed [23].

Antituberculous Agents

Isoniazid

Isoniazid inhibits the metabolism of phenytoin resulting in a 3-fold increase in plasma phenytoin levels. However, this interaction is only relevant in those patients that are “slow metabolizers (acetylators)” of isoniazid (which is genetically determined) and attain sufficiently high plasma isoniazid levels so as to inhibit the metabolism of phenytoin [33, 34].

Rifampicin

Rifampicin enhances the metabolism of phenytoin and can increase mean phenytoin clearance by up to 109 % [35].

When rifampicin and isoniazid are administered in combination, rifampicin counteracts the inhibiting effect of isoniazid on phenytoin metabolism [35].

Antiulcer Drugs

Antacids and Surface-Acting Drugs

Antacids

A significant reduction in phenytoin absorption can occur when phenytoin is co-ingested with calcium-containing and aluminum hydroxide-magnesium salt antacids. However, this has not been a consistent finding in all studies. Factors affecting the extent of interaction include antacid dose, administration times, motility of gastrointestinal tract, and plasma phenytoin levels. To avoid

this interaction, the administration of phenytoin and antacids should be separated by at least 2 h [36].

Sucralfate Phenytoin bioavailability can be decreased by 20 % by sucralfate, but the interaction is avoided when phenytoin is ingested at least 2 h before sucralfate ingestion [37].

Histamine H_2 -Receptor Antagonists

Cimetidine Cimetidine inhibits the metabolism of phenytoin, via an action on CYP2C19, and can increase mean plasma phenytoin AUC values by 20 % [38].

Famotidine Famotidine does not affect the pharmacokinetics of phenytoin [39].

Nizatidine Nizatidine does not affect the pharmacokinetics of phenytoin [40].

Ranitidine With the exception of an isolated case report where phenytoin plasma levels were increased by 50 %, ranitidine has not been found to affect the pharmacokinetics of phenytoin [41, 42].

Proton Pump Inhibitors

Lansoprazole Lansoprazole does not affect the pharmacokinetics of phenytoin [43].

Omeprazole Omeprazole inhibits the metabolism of phenytoin, via an action on CYP2C19, and can increase mean plasma phenytoin AUC values by 25 % [44].

Pantoprazole Pantoprazole does not affect the pharmacokinetics of phenytoin [45].

Antiviral Agents

Acyclovir Acyclovir can decrease plasma phenytoin levels by 71 %. The exact mechanism of this interaction is not known but is considered to be an effect on gastrointestinal absorption [46].

Efavirenz Efavirenz inhibits the metabolism of phenytoin, via an action on CYP2C9 and CYP2C19, and can increase plasma phenytoin levels [47].

***Lopinavir/
ritonavir*** Lopinavir combined with ritonavir enhances the metabolism of phenytoin and can decrease mean plasma phenytoin AUC values by 31 % [48].

Nelfinavir Nelfinavir can decrease plasma phenytoin levels [49].

Nevirapine Nevirapine enhances the metabolism of phenytoin and can decrease plasma phenytoin levels [50].

Ritonavir Ritonavir inhibits the metabolism of phenytoin and can increase plasma phenytoin levels [51].

Zidovudine Zidovudine does not affect the pharmacokinetics of phenytoin [9].

Cardiovascular Drugs

Antiarrhythmics

Amiodarone Amiodarone inhibits the metabolism of phenytoin and can increase plasma phenytoin levels 3-fold [52, 53].

Antihypertensive Agents

<i>Diazoxide</i>	Diazoxide enhances the metabolism of phenytoin and can decrease plasma phenytoin levels to undetectable levels [54].
<i>Diltiazem</i>	Diltiazem can increase phenytoin plasma levels by 90 % [55].
<i>Losartan</i>	Losartan does not affect the pharmacokinetics of phenytoin [56].
<i>Nifedipine</i>	Nifedipine can increase plasma phenytoin levels [57].
<i>Pindolol</i>	Pindolol does not affect the pharmacokinetics of phenytoin [58].
<i>Verapamil</i>	Verapamil can increase plasma phenytoin levels by 20 % [59].

Antiplatelet Drugs

<i>Ticlopidine</i>	Ticlopidine inhibits the metabolism of phenytoin, probably via an action on CYP2C19, and can increase plasma phenytoin levels by 450 % [60].
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Digoxin

<i>Digoxin</i>	Digoxin does not affect the pharmacokinetics of phenytoin [61].
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Lipid-Lowering Drugs

<i>Colestipol</i>	Colestipol does not affect the pharmacokinetics of phenytoin [62].
<i>Cholestyramine</i>	Cholestyramine does not affect the pharmacokinetics of phenytoin [62, 63].

Oral Anticoagulants

<i>Dicoumarol</i>	Dicoumarol can increase plasma phenytoin levels by up to 126 % [64].
<i>Phenindione</i>	Phenindione does not affect the pharmacokinetics of phenytoin [65].
<i>Warfarin</i>	Warfarin does not affect the pharmacokinetics of phenytoin [65].

Herbal Remedies

<i>Grapefruit juice (furanocoumarins)</i>	Grapefruit juice does not affect the pharmacokinetics of phenytoin [66].
<i>Piperine (dried fruits of Piper longum [long pepper], Piper nigrum [black pepper], Zingiber officinale [ginger])</i>	Piperine can inhibit the metabolism of phenytoin, probably via an action on CYP2C9 and/or CYP2C19, and increase mean plasma phenytoin levels by 22 % [67].
<i>Shankhapushpi (ayurvedic preparation)</i>	Shankhapushpi can enhance the metabolism of phenytoin, probably via an action on CYP2C9 and/or CYP2C19, and decreases plasma phenytoin levels. Shankhapushpi also appears to lower seizure threshold [68].

Psychotropic Drugs

Antidepressants

<i>Imipramine</i>	Imipramine can increase plasma phenytoin levels by 68–100 % [69].
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<i>Fluoxetine</i>	Fluoxetine inhibits the metabolism of phenytoin, via an action on CYP2C9, and can increase plasma phenytoin levels by up to 309 % [70].
<i>Fluvoxamine</i>	Fluvoxamine can increase plasma phenytoin levels by up to 200 % [71].
<i>Mirtazapine</i>	Mirtazapine does not affect the pharmacokinetics of phenytoin [72].
<i>Nefazodone</i>	The pharmacokinetics of phenytoin was not altered when given as a single dose to healthy subjects receiving nefazodone [73].
<i>Nortriptyline</i>	Nortriptyline can increase plasma phenytoin levels [74].
<i>Paroxetine</i>	Paroxetine does not affect the pharmacokinetics of phenytoin [75].
<i>Sertraline</i>	Conflicting results have been reported. In one report, sertraline had no effect on the pharmacokinetics of phenytoin while in another sertraline was observed to inhibit the metabolism of phenytoin, via an action on CYP2C9, and to increase plasma phenytoin levels by 187 % [76, 77].
<i>Trazodone</i>	A patient experienced a 158 % increase in plasma phenytoin levels and toxicity during concurrent administration of phenytoin and trazodone [78].
<i>Viloxazine</i>	Viloxazine can increase mean plasma phenytoin levels by 37 % [79].

Antipsychotics

<i>Chlorpromazine</i>	There have been conflicting data on a possible interaction of chlorpromazine with phenytoin, with no change, a decrease or an increase in plasma
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- phenytoin level having all been reported [74, 80, 81].
- Loxapine*** Loxapine can decrease plasma phenytoin levels [82].
- Risperidone*** Risperidone inhibits the metabolism phenytoin, probably via an action on CYP2C9, and can increase plasma phenytoin levels [83].
- Thioridazine*** A variable effect is seen with an increase in plasma phenytoin levels and neurotoxicity in some patients, a decrease in plasma phenytoin levels in others, and with most patients experiencing no change in plasma phenytoin levels after the addition of thioridazine [84, 85].

Steroids

- Dexamethasone*** The effects of dexamethasone on the pharmacokinetics of phenytoin are conflicting, with both a decrease in plasma phenytoin levels (30–50 %) and an increase in plasma phenytoin levels (38 %) observed [86–88].
- Danazol*** The effects of danazol on the pharmacokinetics of phenytoin are conflicting with both an increase and a decrease in plasma phenytoin levels observed [89].

Miscellanea

- Allopurinol*** Allopurinol inhibits the metabolism of phenytoin and can increase mean plasma phenytoin AUC values by 50–120 % and mean plasma phenytoin levels can increase by 26–37 % [90].

<i>Atovaquone</i>	Atovaquone does not affect the pharmacokinetics of phenytoin [91].
<i>Azapropazone</i>	Azapropazone inhibits the metabolism of phenytoin and can decrease phenytoin clearance by 35–59 % and can increase plasma phenytoin levels at least 2-fold [92].
<i>Chlorphenamine</i> (<i>Chlorpheniramine</i>)	Chlorphenamine inhibits phenytoin metabolism and can increase plasma phenytoin levels [93, 94].
<i>Diazepam</i>	Data are conflicting with case reports and controlled studies reporting both increases and decreases in plasma phenytoin levels [80, 95].
<i>Disulfiram</i>	Disulfiram inhibits the metabolism of phenytoin and can increase mean plasma phenytoin half-life values by 73 %, decrease mean plasma phenytoin clearance values by 66 %, and increase plasma phenytoin levels by 100–400 % [96, 97].
<i>Flunarizine</i>	Flunarizine does not affect the pharmacokinetics of phenytoin [98].
<i>Methaqualone</i> (<i>Mandrax</i>)	Methaqualone can increase plasma phenytoin levels [99].
<i>Methylphenidate</i>	The effects of methylphenidate on the pharmacokinetics of phenytoin are conflicting, with both an increase in plasma phenytoin levels and no effect observed [100–102].
<i>Orlistat</i>	Orlistat does not affect the pharmacokinetics of phenytoin [103].
<i>Sulfinpyrazone</i>	Sulfinpyrazone inhibits the metabolism of phenytoin and can increase plasma phenytoin levels by 100 % [104].

<i>Tacrolimus</i>	Tacrolimus can increase plasma phenytoin levels by 97 % [105].
<i>Theophylline</i>	Theophylline can decrease phenytoin plasma levels by 21 %. The interaction may be attributable to diminished oral absorption [106].
<i>Tolazamide</i>	Tolazamide does not affect the pharmacokinetics of phenytoin [107].
<i>Tolbutamide</i>	Tolbutamide can cause a transient 45 % increase in free nonprotein-bound plasma phenytoin levels and a 10 % decrease in total phenytoin plasma levels [107, 108].
<i>Zileuton</i>	Zileuton does not affect the pharmacokinetics of phenytoin [109].

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Piracetam

There have been no reports of the effect of non-AED drugs on the pharmacokinetics or pharmacodynamics of piracetam.

Pregabalin

<i>Furosemide</i>	Furosemide does not affect the pharmacokinetics of pregabalin [1].
<i>Glibenclamide (glyburide)</i>	Glibenclamide does not affect the pharmacokinetics of pregabalin [1].
<i>Glimepiride</i>	Glimepiride does not affect the pharmacokinetics of pregabalin [1].
<i>Glipizide</i>	Glipizide does not affect the pharmacokinetics of pregabalin [1].
<i>Insulin</i>	Insulin does not affect the pharmacokinetics of pregabalin [1].
<i>Metformin</i>	Metformin does not affect the pharmacokinetics of pregabalin [1].
<i>Oral contraceptives</i>	Oral contraceptives do not affect the pharmacokinetics of pregabalin [2].

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Primidone

<i>Bleomycin</i>	Bleomycin does not affect the pharmacokinetics of primidone [1].
<i>Isoniazid</i>	Isoniazid inhibits the metabolism of primidone and can increase plasma primidone levels by 83 % and decrease plasma phenobarbital levels by 12 % [2].
<i>Danazol</i>	Danazol does not affect the pharmacokinetics of primidone [3].
<i>Nicotinamide</i>	Nicotinamide inhibits the metabolism of primidone to phenobarbital and can increase the plasma primidone/phenobarbital ratio [4].
<i>Special note</i>	As primidone is metabolized to phenobarbital, all the interactions highlighted for phenobarbital will also apply to primidone.

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Retigabine

There have been no reports of the effect of non-AED drugs on the pharmacokinetics or pharmacodynamics of retigabine.

Rufinamide

There have been no reports of the effect of non-AED drugs on the pharmacokinetics or pharmacodynamics of rufinamide.

Stiripentol

There have been no reports of the effect of non-AED drugs on the pharmacokinetics or pharmacodynamics of stiripentol.

Sulthiame

Antacids

Antacids containing magnesium trisilicate can decrease the oral bioavailability of sulthiame by up to 73 %, while antacids containing bismuth oxycarbonate and magnesium oxide can decrease the oral bioavailability of sulthiame by <105 %. To avoid problems, administration of sulthiame and antacids should be separated by at least 2 h [1].

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Tiagabine

<i>Cimetidine</i>	Cimetidine can increase mean plasma tiagabine AUC values and mean plasma tiagabine levels by 5 % [1].
<i>Digoxin</i>	Digoxin does not affect the pharmacokinetics of tiagabine [2].
<i>Erythromycin</i>	Erythromycin does not affect the pharmacokinetics of tiagabine [3].
<i>Gemfibrozil</i>	Gemfibrozil can increase mean plasma tiagabine levels by 59–75 % [4].
<i>Theophylline</i>	Theophylline does not affect the pharmacokinetics of tiagabine [1].
<i>Triazolam</i>	Triazolam does not affect the pharmacokinetics of tiagabine [5].
<i>Warfarin</i>	Warfarin does not affect the pharmacokinetics of tiagabine [1].

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Topiramate

<i>Amitriptyline</i>	Amitriptyline can decrease the clearance of topiramate [1].
<i>Dihydroergotamine</i>	Dihydroergotamine does not affect the pharmacokinetics of topiramate [1].
<i>Diltiazem</i>	Diltiazem can increase mean plasma topiramate AUC values by 20 % [2].
<i>Flunarizine</i>	Flunarizine does not affect the pharmacokinetics of topiramate [2].
<i>Glibenclamide (glyburide)</i>	Glibenclamide does not affect the pharmacokinetics of topiramate [2].
<i>Hydrochlorothiazide</i>	Hydrochlorothiazide can increase mean plasma topiramate C _{max} values by 27 % and mean plasma topiramate AUC values by 29 % [2].
<i>Lithium</i>	Lithium can decrease the clearance of topiramate [1].
<i>Metformin</i>	Metformin can decrease the clearance of topiramate [2].
<i>Pizotifen</i>	Pizotifen does not affect the pharmacokinetics of topiramate [2].
<i>Propranolol</i>	Propranolol can decrease mean plasma topiramate clearance values by 14 %

	and increase mean plasma topiramate AUC values 17 % [1].
<i>Posaconazole</i>	Posaconazole inhibits topiramate metabolism, probably via an action on CYP3A4, and can increase plasma topiramate levels by 137 %. [3]
<i>Sumatriptan</i>	Sumatriptan can decrease the clearance of topiramate [1].
<i>Temozolomide</i>	Temozolomide does not affect the pharmacokinetics of topiramate [4].
<i>Venlafaxine</i>	Venlafaxine does not affect the pharmacokinetics of topiramate [1].

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Valproic Acid

Analgesics

Aspirin

Salicylic acid displaces valproic acid from plasma protein binding sites (primarily albumin) and can inhibit valproic acid metabolism, via the β -oxidation pathway, by 66 %. Concurrent administration of an antipyretic dose of aspirin to children can result in a 23 % increase in free nonprotein-bound plasma valproic acid levels. In this setting, clinical management may best be guided by measurement of free phenytoin levels [1, 2].

Diffenital

Diffenital can increase the clearance of valproic acid and decrease plasma valproic acid levels. These changes are the consequence of an interaction at the renal level whereby diffenital interferes with the renal excretion of at least three of the metabolites of valproic acid [3].

Naproxen

Naproxen can decrease mean plasma valproic acid levels by 20 %, increase

mean plasma valproic acid clearance values by 22 %, and increase the mean valproic acid unbound fraction by 20 %. These changes are the consequence of valproic acid protein binding displacement by naproxen [4].

Antibacterials

<i>Amikacin</i>	Amikacin can decrease plasma valproic acid levels, probably via an induction of valproic acid metabolism [5].
<i>Doripenem</i>	Doripenem can decrease plasma valproic acid levels by 69 %. The mechanism of this interaction is unknown but may involve induction of metabolism via an action on UGT1A [6].
<i>Ertapenem</i>	Ertapenem can decrease plasma valproic acid levels by >99 %. The mechanism of this interaction is unknown but may involve induction of metabolism via an action on UGT1A [7].
<i>Erythromycin</i>	Two single cases of an increase in valproic acid plasma levels and toxicity following the addition of erythromycin have been reported [8, 9].
<i>Imipenem</i>	Imipenem can decrease plasma valproic acid levels by >99 %. The mechanism of this interaction is unknown but may involve induction of metabolism via an action on UGT1A [10].
<i>Meropenem</i>	Meropenem can decrease mean plasma valproic acid levels by 82 %. The mechanism of this interaction is unknown but may involve induction of metabolism via an action on UGT1A [11].
<i>Panipenem</i>	Panipenem can decrease plasma valproic acid levels by >99 %. The mecha-

nism of this interaction is unknown but may involve induction of metabolism via an action on UGT1A [12].

Antifungal Agents

Posaconazole Posaconazole does not affect the pharmacokinetics of valproic acid [13].

Antineoplastic Agents

Cisplatin Cisplatin can decrease plasma valproic acid levels by 50 % [14].

Methotrexate Methotrexate can decrease plasma valproic acid levels by 75 %. The exact mechanism is unknown. Possible mechanisms include plasma protein binding displacement or a decrease in valproic acid absorption [15].

Antituberculous Agents

Isoniazid Isoniazid inhibits the metabolism of valproic acid and can increase plasma valproic acid levels [16].

Rifampicin Rifampicin enhances the metabolism of valproic acid and can decrease plasma valproic acid levels [9].

Antiulcer Drugs

Antacids and Surface-Acting Drugs

Antacids A single-dose study in healthy volunteers evaluated the effect of three

antacid preparations on valproic acid absorption. While no significant change in extent of absorption occurred with some antacids (e.g., aluminum hydroxide/magnesium trisilicate, or calcium carbonate), concurrent administration of another (aluminum hydroxide/magnesium hydroxide) produced a small (mean 12 %; range 3–28 %) but statistically significant increase in mean plasma valproic acid AUC values [17].

Histamine H₂-Receptor Antagonists

<i>Cimetidine</i>	Cimetidine can increase plasma valproic acid clearance by 2–17 % [18].
<i>Ranitidine</i>	Ranitidine does not affect the pharmacokinetics of valproic acid [18].

Antiviral Agents

<i>Acyclovir</i>	Acyclovir can decrease plasma valproic acid levels by 33 %. The exact mechanism of this interaction is not known but is thought to be an effect on gastrointestinal absorption [19].
<i>Efavirenz</i>	Efavirenz can decrease plasma valproic acid levels by >50 % [20].
<i>Lopinavir/ ritonavir</i>	Lopinavir combined with ritonavir does not affect the pharmacokinetics of valproic acid [21].
<i>Ritonavir</i>	Ritonavir enhances the metabolism of valproic acid, via induction of glucuronyltransferases, and can decrease plasma valproic levels by 48 % [22].

Cardioactive Drugs

<i>Propranolol</i>	Propranolol does not affect the pharmacokinetics of valproic acid [23].
<i>Verapamil</i>	Verapamil can increase plasma valproic acid levels by 155 % [24].

Psychoactive Drugs

Antidepressants

<i>Bupropion</i>	Bupropion can increase plasma valproic acid levels [25].
<i>Lithium</i>	Lithium can increase plasma valproic acid AUC values by 11 % and plasma valproic acid levels by 7 % [26].
<i>Fluoxetine</i>	Anecdotal reports in two patients suggest that fluoxetine causes an increase in plasma valproic acid levels. In contrast, two cases of decreased plasma valproic acid levels have also been reported [27–29].
<i>Paroxetine</i>	Paroxetine does not affect the pharmacokinetics of valproic acid [30].
<i>Sertraline</i>	Sertraline can increase plasma valproic acid levels 3-fold [31].

Antipsychotics

<i>Aripiprazole</i>	Aripiprazole does not affect the pharmacokinetics of valproic acid [32].
<i>Chlorpromazine</i>	Chlorpromazine can decrease mean plasma valproic acid clearance values by 14 %, increase mean plasma elimination half-life values by 14 %, and increase mean plasma valproic acid levels by 22 % [33].

Haloperidol

Haloperidol does not affect the pharmacokinetics of valproic acid [33].

Quetiapine

It is not known whether quetiapine affects the pharmacokinetics of valproic acid.

Cases of delirium have been reported when quetiapine was added to valproic acid. This effect is probably the consequence of a pharmacodynamic interaction [34].

Zotepine

It is not known whether zotepine affects the pharmacokinetics of valproic acid.

A case of delirium has been reported when zotepine was added to valproic acid. This effect is probably the consequence of a pharmacodynamic interaction [35].

CNS Stimulants and Drugs Used for Attention Deficit Disorders

Methylphenidate

Methylphenidate does not affect the pharmacokinetics of valproic acid [36].

Adverse effects comprising of dyskinesia and bruxism can occur during methylphenidate and valproic acid combination therapy which is considered to be the consequence of a pharmacodynamic interaction [36].

Steroids

Danazol

The effects of danazol on the pharmacokinetics of valproic acid are conflicting with both an increase and a decrease in plasma valproic acid levels observed [37].

**Oral
contraceptives**

Oral contraceptives enhance the metabolism of valproic acid and can decrease plasma total and free valproic acid levels by 18 and 29 %, respectively [38].

Miscellanea***Cholestyramine***

Cholestyramine decreases the absorption of valproic acid and decrease mean plasma valproic acid AUC values by 15 %. This interaction can be avoided by separating the administration of valproic acid and cholestyramine by at least 3 h [39, 40].

Guanfacine

Guanfacine inhibits the metabolism of valproic acid, via an action on glucuronidation, and can increase valproic acid plasma levels by 68 % [41].

Oxiracetam

Oxiracetam does not affect the pharmacokinetics of valproic acid [42].

***Paeoniae Radix
(Chinese
medicine)***

Paeoniae Radix does not affect the pharmacokinetics of valproic acid [43].

Theophylline

Theophylline does not affect the pharmacokinetics of valproic acid [44].

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Vigabatrin

There have been no reports on the effects of non-AED drugs on the pharmacokinetics or pharmacodynamics of vigabatrin.

Zonisamide

<i>Cimetidine</i>	Cimetidine does not affect the pharmacokinetics of zonisamide [1].
<i>Risperidone</i>	Risperidone can decrease plasma zonisamide levels by 55 % [2].
<i>Ritonavir</i>	Ritonavir does not affect the pharmacokinetics of zonisamide [3].

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Part III
Drug Interactions Between
AEDs and Non-AED Drugs:
Interactions Affected by AEDs

Analgesics

Codeine

Carbamazepine Carbamazepine enhances the metabolism of codeine and decreases plasma codeine levels [1].

Diflunisal

Valproic Acid Valproic acid does not affect the pharmacokinetics of diflunisal [2].

Fentanyl

Carbamazepine Carbamazepine enhances the metabolism of fentanyl so that a higher fentanyl dosage is required in order to maintain anesthesia [3].

Phenobarbital Phenobarbital enhances the metabolism of fentanyl so that a higher fentanyl dosage is required in order to maintain anesthesia [3].

Phenytoin Phenytoin enhances the metabolism of fentanyl so that a higher fentanyl dosage is required in order to maintain anesthesia [3].

Primidone Primidone enhances the metabolism of fentanyl so that a higher fentanyl dosage is required in order to maintain anesthesia [3].

Meperidine (Pethidine)

Phenobarbital Phenobarbital enhances the metabolism of meperidine so that plasma meperidine levels are decreased while plasma levels of normeperidine, its pharmacologically active metabolite that has a lower analgesic potency but greater toxicity than meperidine, are increased [4].

An increase in meperidine toxicity may be attributable to the increased plasma levels of normeperidine, its pharmacologically active metabolite [5].

Phenytoin Phenytoin enhances the metabolism of meperidine and can increase mean plasma meperidine clearance values by 20 % and decrease mean plasma meperidine AUC values by 50 % [6].

Methadone

Carbamazepine Carbamazepine enhances the metabolism of methadone and can decrease plasma methadone levels [7].

Phenobarbital Phenobarbital enhances the metabolism of methadone and can decrease plasma methadone levels [8].

Phenytoin Phenytoin enhances the metabolism of methadone and can decrease plasma methadone levels [9].

Valproic Acid Valproic acid does not affect the pharmacokinetics of methadone [10].

Morphine

Gabapentin Gabapentin does not affect the pharmacokinetics of morphine [11].

A pharmacodynamic interaction also occurs whereby gabapentin enhances the analgesic effect of morphine [11].

Naproxen

Gabapentin Gabapentin does affect the pharmacokinetics of naproxen [12].

Valproic Acid Valproic acid inhibits the metabolism of naproxen, via an action on glucuronidation, and can decrease mean plasma naproxen clearance values by 7 % and increase mean plasma naproxen AUC values by 7 % [13].

Paracetamol

Carbamazepine Carbamazepine enhances the metabolism of paracetamol, probably via an action on CYP1A2, and can increase mean plasma paracetamol clearance by 52 % and decrease mean plasma paracetamol AUC values by 39 % [14].

Phenobarbital Phenobarbital enhances the metabolism of paracetamol, probably via an action

Phenytoin

on CYP1A2, and can increase mean plasma paracetamol clearance by 52 % and decrease mean plasma paracetamol AUC values by 39 % [14].

Phenytoin enhances the metabolism of paracetamol, probably via an action on CYP1A2, and can decrease plasma paracetamol AUC values by 40 % and increase plasma paracetamol clearance by 52 %. Plasma paracetamol levels can be decreased by up to 75 % [15].

Primidone

Primidone enhances the metabolism of paracetamol, probably via an action on CYP1A2, and can increase mean plasma paracetamol clearance by 52 % and decrease mean plasma paracetamol AUC values by 39 % [14].

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Antimicrobials

Antibacterials

Chloramphenicol

Phenobarbital Phenobarbital enhances the metabolism of chloramphenicol and can decrease plasma chloramphenicol levels by 70–95 % [1].

Phenytoin Phenytoin inhibits the metabolism of chloramphenicol and can increase mean plasma chloramphenicol half-life values by 14 % and mean plasma chloramphenicol levels by 15 % [2].

Clinafloxacin

Phenytoin Phenytoin does not affect the pharmacokinetics of clinafloxacin [3].

Doxycycline

- Carbamazepine*** Carbamazepine enhances the metabolism of doxycycline and can decrease mean plasma doxycycline half-life values by 44 % [4].
- Phenobarbital*** Phenobarbital enhances the metabolism of doxycycline and can decrease plasma doxycycline levels [5].
- Phenytoin*** Phenytoin enhances the metabolism of doxycycline and can decrease the mean elimination half-life of doxycycline by 52 % [4].

Rifampicin

- Phenobarbital*** Phenobarbital enhances the metabolism of rifampicin and can decrease plasma rifampicin levels by 20–40 % [6].

Metronidazole

- Phenobarbital*** Phenobarbital enhances the metabolism of metronidazole and can increase plasma metronidazole clearance by 50 % and decrease plasma metronidazole AUC values by 33 % [7].

Antifungal Agents

Griseofulvin

- Phenobarbital*** A decrease in the plasma level and clinical effectiveness of griseofulvin has been reported in patients taking

phenobarbital. Interestingly, this interaction may not necessarily involve enzyme induction, as there is evidence that phenobarbital may impair the absorption of this antifungal [8].

Fluconazole

Phenytoin

Phenytoin does not affect the pharmacokinetics of fluconazole [9].

Itraconazole

Carbamazepine

Carbamazepine enhances the metabolism of itraconazole, probably via an action on CYP3A4, and can decrease plasma itraconazole levels so that they are not detectable [10].

Phenobarbital

Phenobarbital enhances the metabolism of itraconazole, probably via an action on CYP3A4, and can decrease plasma itraconazole levels [11].

Phenytoin

Phenytoin enhances the metabolism of itraconazole, probably via an action on CYP3A4, and can decrease mean plasma itraconazole AUC values by 93 % and decrease mean plasma itraconazole half-life values by 83 % [12].

Ketoconazole

Carbamazepine

Carbamazepine enhances the metabolism of ketoconazole, probably via an action on CYP3A4, and can decrease plasma ketoconazole levels so that they are not detectable [10].

Phenytoin Phenytoin enhances the metabolism of ketoconazole, probably via an action on CYP3A4, and can decrease plasma ketoconazole levels so that they are not detectable [10].

Posaconazole

Phenytoin Phenytoin enhances the metabolism of posaconazole, probably via an action on UGT1A4, and can decrease mean plasma posaconazole AUC values by 52 % [13].

Voriconazole

Phenytoin Phenytoin enhances the metabolism of voriconazole, via an action on CYP2C9 and possibly CYP2C19, and can decrease mean plasma voriconazole AUC values by ~70 % [14].

Antihelmintics

Albendazole

Carbamazepine Carbamazepine enhances the metabolism of albendazole, probably via an action on CYP3A4, and can decrease mean plasma albendazole AUC and plasma albendazole half-life values by 50 % and can decrease plasma albendazole levels by 50 % [15].

Phenobarbital Phenobarbital enhances the metabolism of albendazole, probably via an action

Phenytoin on CYP3A4, and can decrease mean plasma albendazole AUC values by 71 % and plasma albendazole half-life values by 39 % and can decrease plasma albendazole levels by 63 % [15]. Phenytoin enhances the metabolism of albendazole, probably via an action on CYP3A4, and can decrease mean plasma albendazole AUC values by 66 % and plasma albendazole half-life values by 53 % and can decrease plasma albendazole levels by 63 % [15].

Mebendazole

Carbamazepine Carbamazepine enhances the metabolism of mebendazole and can decrease plasma mebendazole levels [16].

Phenytoin Phenytoin enhances the metabolism of mebendazole and can decrease plasma mebendazole levels [16].

Praziquantel

Carbamazepine Carbamazepine enhances the first-pass metabolism of praziquantel and can decrease plasma praziquantel half-life values by 88 % and can decrease plasma praziquantel levels by 90 % [17].

Phenytoin Phenytoin enhances the first-pass metabolism of praziquantel and can decrease plasma praziquantel half-life values by 86 % and can decrease plasma praziquantel levels by 74 % [17].

Antituberculous Agents

Isoniazid

Carbamazepine Carbamazepine enhances the metabolism of acetylhydrazine, a major metabolite of isoniazid, to a reactive intermediate, thereby contributing to isoniazid-associated hepatotoxicity [18].

Antiviral Agents

Atazanavir

Valproic Acid Valproic acid does not affect the pharmacokinetics of atazanavir [19].

Delavirdine

Phenytoin Phenytoin enhances the metabolism of delavirdine and can decrease plasma delavirdine levels [20]

Phenobarbital Phenobarbital enhances the metabolism of delavirdine and can decrease plasma delavirdine levels [20].

Efavirenz

Carbamazepine Carbamazepine enhances the metabolism of efavirenz, via an action on CYP3A4, and can decrease mean plasma efavirenz C_{max} values by 21 % and mean plasma efavirenz AUC values by 36 % [21].

Phenytoin Phenytoin enhances the metabolism of efavirenz, via an action on CYP3A4, and can decrease plasma efavirenz levels [22].

<i>Valproic Acid</i>	Valproic acid does not affect the pharmacokinetics of efavirenz [23].
<i>Indinavir</i>	
<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of indinavir, via an action on CYP3A4, and can decrease plasma indinavir levels by 25 % [24].
<i>Lersivirine</i>	
<i>Valproic Acid</i>	Valproic acid inhibits the metabolism of lersivirine, via an action on UGT2B7, and can increase mean plasma lersivirine AUC values by 25 % [25].
<i>Lopinavir</i>	
<i>Lamotrigine</i>	Lamotrigine does not affect the pharmacokinetics of lopinavir and low-dose ritonavir [26].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of lopinavir and can decrease mean plasma lopinavir AUC values by 33 % [27, 28].
<i>Valproic Acid</i>	Valproic acid can increase mean plasma lopinavir AUC values by 38 % [23].
<i>Nevirapine</i>	
<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of nevirapine, via an action on CYP3A4, and can decrease mean plasma nevirapine half-life values by 37 % and decreases plasma nevirapine levels [29].

Phenytoin Phenytoin enhances the metabolism of nevirapine, via an action on CYP3A4, and can decrease plasma nevirapine levels [29].

Phenobarbital Phenobarbital does not affect the pharmacokinetics of nevirapine [29].

Raltegravir

Lamotrigine Lamotrigine does not affect the pharmacokinetics of raltegravir [30].

Ritonavir

Lamotrigine Lamotrigine does not affect the pharmacokinetics of low-dose ritonavir when administered in combination with lopinavir [26].

Phenytoin Phenytoin enhances the metabolism of ritonavir and can decrease mean plasma ritonavir AUC values by 28 % [27, 28].

Valproic Acid Valproic acid does not affect the pharmacokinetics of ritonavir [19].

Saquinavir

Stiripentol Stiripentol does not affect the pharmacokinetics of saquinavir [31, 32].

Zidovudine

Phenytoin Phenytoin does not affect the pharmacokinetics of zidovudine [33].

Valproic Acid Valproic acid inhibits the metabolism of zidovudine, via an action on glucuronidation, and can increase plasma zidovudine levels by 100 % [34].

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Antineoplastic Agents

9-Aminocamptothecin

<i>Carbamazepine</i>	Carbamazepine enhances the mean plasma clearance of 9-aminocamptothecin by 68 % and can decrease median plasma 9-aminocamptothecin levels by 67 % [1].
<i>Phenobarbital</i>	Phenobarbital enhances the mean plasma clearance of 9-aminocamptothecin by 68 % and can decrease median plasma 9-aminocamptothecin levels by 67 % [1].
<i>Phenytoin</i>	Phenytoin enhances the mean plasma clearance of 9-aminocamptothecin by 68 % and can decrease median plasma 9-aminocamptothecin levels by 67 % [1].

Busulphan

<i>Phenytoin</i>	Phenytoin enhances the metabolism of busulphan and can increase mean plasma busulphan clearance by 19 %, decrease mean plasma busulphan elimination half-life values by 23 %, and decrease mean plasma busulphan AUC values by 16 % [2].
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CCNU (1-(2-Chloroethyl)-3-Cyclohexyl-1-Nitrosourea)

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of CCNU [3].
<i>Lamotrigine</i>	Lamotrigine does not affect the pharmacokinetics of CCNU [3].
<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of CCNU [3].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of CCNU [3].
<i>Valproic Acid</i>	Valproic acid does not affect the pharmacokinetics of CCNU [3].

Celecoxib

<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of celecoxib [4].
<i>Phenytoin</i>	Phenytoin does not affect the pharmacokinetics of celecoxib [4].

Cisplatin

<i>Valproic Acid</i>	Valproic acid in combination with cisplatin is associated with a 3-fold higher incidence of reversible thrombopenia, neutropenia, or both. This is considered to be a consequence of a pharmacodynamic interaction, and this interaction may also occur with etoposide and fotemustine [5].
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Cyclophosphamide

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of cyclophosphamide, a pharmaco-
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- logically inactive prodrug, to the pharmacologically active metabolite 4-hydroxycyclophosphamide. Plasma 4-hydroxycyclophosphamide AUC values can increase by 58 %, while plasma cyclophosphamide AUC values can decrease by 40 % [6].
- Phenytoin** Phenytoin enhances the metabolism of cyclophosphamide, a pharmacologically inactive prodrug, to the pharmacologically active metabolite 4-hydroxycyclophosphamide. Plasma 4-hydroxycyclophosphamide AUC values can increase by 51 %, while plasma 4-hydroxycyclophosphamide C_{max} values can increase by 6-fold [7].

Cytarabine

- Carbamazepine** Carbamazepine does not affect the pharmacokinetics of cytarabine [8].
- Phenobarbital** Phenobarbital does not affect the pharmacokinetics of cytarabine [8].
- Phenytoin** Phenytoin does not affect the pharmacokinetics of cytarabine [8].

Etoposide

- Phenobarbital** Phenobarbital enhances the metabolism of etoposide and can increase mean plasma etoposide clearance by 77 % and decrease mean plasma etoposide half-life values by 18 % [9].
- Phenytoin** Phenytoin enhances the metabolism of etoposide and can increase mean plasma etoposide clearance by 77 % and decrease mean plasma etoposide half-life values by 18 % [9].

Gefitinib

Phenytoin Phenytoin enhances the metabolism of gefitinib and can decrease plasma gefitinib clearance by 2.3-fold and mean plasma gefitinib C_{max} and AUC values by 36 and 52 %, respectively [10].

Glufosfamide

Carbamazepine Carbamazepine enhances the plasma clearance glufosfamide by up to 15 % and can decrease plasma glufosfamide AUC values by up to 15 % [11].

Oxcarbazepine Oxcarbazepine enhances the plasma clearance glufosfamide by up to 15 % and can decrease plasma glufosfamide AUC values by up to 15 % [11].

Phenobarbital Phenobarbital enhances the plasma clearance glufosfamide by up to 15 % and can decrease plasma glufosfamide AUC values by up to 15 % [11].

Phenytoin Phenytoin enhances the plasma clearance glufosfamide by up to 15 % and can decrease plasma glufosfamide AUC values by up to 15 % [11].

Ifosfamide

Phenobarbital Phenobarbital does not affect the pharmacokinetics of ifosfamide [12].

A pharmacodynamic interaction between phenytoin and ifosfamide, resulting in encephalopathy, may occur [13].

Phenytoin Phenytoin enhances the metabolism of ifosfamide. In general, this interaction

would be expected to result in decreased efficacy of ifosfamide. However, because the metabolism of ifosfamide results in a pharmacologically active metabolite, enzyme induction could theoretically potentiate drug effects by stimulating bioactivation processes [14].

Imatinib

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of imatinib and can decrease mean plasma imatinib levels by 66 % [15].
<i>Lamotrigine</i>	Lamotrigine does not affect the pharmacokinetics of imatinib [15].
<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of imatinib [15].
<i>Oxcarbazepine</i>	Oxcarbazepine enhances the metabolism of imatinib and can decrease mean plasma imatinib levels by 62 % [15].
<i>Topiramate</i>	Topiramate enhances the metabolism of imatinib and can decrease mean plasma imatinib levels by 49 % [15].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of imatinib and can decrease mean plasma imatinib levels by 73 % [15].
<i>Primidone</i>	Primidone enhances the metabolism of imatinib and can decrease plasma imatinib levels [16].
<i>Valproic Acid</i>	Valproic acid does not affect the pharmacokinetics of imatinib [15].

Irinotecan

<i>Phenytoin</i>	Phenytoin enhances the metabolism of irinotecan, a prodrug which is metabolized to a pharmacologically
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active metabolite 7-ethyl-10-hydroxy-camptothecin, via carboxylesterases, and to an inactive metabolite APC, via an action on CYP3A4. 7-ethyl-10-hydroxy-camptothecin is further metabolized by glucuronidation, primarily via UGT1A1. Mean plasma irinotecan AUC values decrease by 26 %, while mean plasma 7-ethyl-10-hydroxy-camptothecin and APC AUC values decrease by 53 % and increase by 17 %, respectively [17].

Phenobarbital

Phenobarbital enhances the metabolism of irinotecan, a prodrug which is metabolized to a pharmacologically active metabolite 7-ethyl-10-hydroxy-camptothecin, via carboxylesterases, and to an inactive metabolite APC, via an action on CYP3A4. 7-ethyl-10-hydroxy-camptothecin is further metabolized by glucuronidation, primarily via UGT1A1. Mean plasma 7-ethyl-10-hydroxy-camptothecin AUC values decrease by 75 % [18].

Primidone

Primidone enhances the metabolism of irinotecan, a prodrug which is metabolized to a pharmacologically active metabolite 7-ethyl-10-hydroxy-camptothecin, via carboxylesterases, and to an inactive metabolite APC, via an action on CYP3A4. 7-ethyl-10-hydroxy-camptothecin is further metabolized by glucuronidation, primarily via UGT1A1. Mean plasma 7-ethyl-10-hydroxy-camptothecin clearance values decrease by 37 % [19].

Valproic Acid

Valproic acid interacts with irinotecan, a prodrug which is metabolized to a pharmacologically active metabolite 7-ethyl-10-hydroxy-camptothecin, via

carboxylesterases, and to an inactive metabolite APC, via an action on CYP3A4. 7-ethyl-10-hydroxy-camptothecin is further metabolized by glucuronidation, primarily via UGT1A1. Mean plasma irinotecan, 7-ethyl-10-hydroxy-camptothecin, and glucuronide metabolite AUC values decrease by 16, 43 and 33 %, respectively. The exact mechanism of these effects is not known but may be due to a combination of induction of UGT1A1 metabolism and a plasma protein binding displacement interaction involving 7-ethyl-10-hydroxy-camptothecin [20].

Lapatinib

Carbamazepine Carbamazepine enhances the metabolism of lapatinib, via an action on CYP3A4, and decreases mean plasma AUC lapatinib values by 72 %. A concurrent 28 % mean decrease in lapatinib absorption also occurs, probably via an action on ABCB2 transporter [21].

Methotrexate

Carbamazepine Carbamazepine enhances the metabolism of methotrexate and can increase plasma methotrexate clearance by up to 55 % [8].

Phenobarbital Phenobarbital enhances the metabolism of methotrexate and can increase plasma methotrexate clearance by up to 55 % [8].

<i>Phenytoin</i>	Phenytoin enhances the metabolism of methotrexate and can increase plasma methotrexate clearance by up to 55 % [8].
<i>Topiramate</i>	Topiramate does not affect the metabolism of methotrexate [22].

Paclitaxel

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of paclitaxel and can increase mean plasma paclitaxel clearance by 101 % and decrease mean plasma paclitaxel AUC values by 52 % [23].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of paclitaxel and can increase mean plasma paclitaxel clearance by 101 % and decrease mean plasma paclitaxel AUC values by 52 % [23].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of paclitaxel and can increase mean plasma paclitaxel clearance by 101 % and decrease mean plasma paclitaxel AUC values by 52 % [23].
<i>Valproic Acid</i>	Valproic acid inhibits the metabolism of paclitaxel and can decrease plasma paclitaxel clearance by 26 % and increase plasma paclitaxel AUC values by 40 % [23].

Procarbazine

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of procarbazine and increases procarbazine hypersensitivity reactions, possibly through an intermediate metabolite generated by the induction of a CYP3A isoform [24].
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<i>Gabapentin</i>	Gabapentin does not affect the pharmacokinetics of procarbazine [25].
<i>Lamotrigine</i>	Lamotrigine does not affect the pharmacokinetics of procarbazine [25].
<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of procarbazine [25].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of procarbazine and increases procarbazine hypersensitivity reactions, possibly through an intermediate metabolite generated by the induction of a CYP3A isoform [24].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of procarbazine and increases procarbazine hypersensitivity reactions, possibly through an intermediate metabolite generated by the induction of a CYP3A isoform [24].
<i>Topiramate</i>	Topiramate does not affect the pharmacokinetics of procarbazine [25].
<i>Valproic Acid</i>	Valproic acid does not affect the pharmacokinetics of procarbazine [25].

Temozolomide

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of temozolomide and can decrease plasma temozolomide levels [3].
<i>Lamotrigine</i>	Lamotrigine does not affect the pharmacokinetics of temozolomide [3].
<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of temozolomide [3].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of temozolomide and can decrease plasma temozolomide levels [3].
<i>Valproic Acid</i>	Valproic acid does not affect the pharmacokinetics of temozolomide [3].

Temsirolimus

- Carbamazepine*** Carbamazepine enhances the metabolism of temsirolimus so that after IV administration, mean plasma C_{max} values are decreased by 36 %. Additionally, mean plasma C_{max} and AUC values for the pharmacologically active metabolite, sirolimus, are decreased by 67 and 43 %, respectively [26].
- Phenytoin*** Phenytoin enhances the metabolism of temsirolimus so that after IV administration, mean plasma C_{max} values are decreased by 36 %. Additionally, mean plasma C_{max} and AUC values for the pharmacologically active metabolite, sirolimus, are decreased by 67 and 43 %, respectively [26].

Teniposide

- Carbamazepine*** Carbamazepine enhances the metabolism of teniposide, via an action on CYP3A4, and can increase plasma teniposide clearance by 100 % and decrease plasma teniposide levels [8].
- Phenobarbital*** Phenobarbital enhances the metabolism of teniposide, via an action on CYP3A4, and can increase mean plasma teniposide clearance by 146 % and decrease plasma teniposide levels [27].
- Phenytoin*** Phenytoin enhances the metabolism of teniposide, via an action on CYP3A4, and can increase plasma teniposide clearance by 217 % and decrease plasma teniposide levels [27].

Thiotepa

Carbamazepine

Carbamazepine enhances the metabolism of thiotepa, via an action on CYP2B6 and CYP3A4, resulting in an increase in the equipotent pharmacologically active metabolite tepa. Plasma tepa AUC values are increased by 75 %, while plasma thiotepa AUC values are decreased by 43 % [6].

Phenytoin

Phenytoin enhances the metabolism of thiotepa, via an action on CYP2B6 and CYP3A4, resulting in an increase in the equipotent pharmacologically active metabolite tepa. Mean plasma tepa AUC values are increased by 115 % [28].

Topotecan

Phenytoin

Phenytoin enhances the metabolism of topotecan and can increase mean plasma topotecan clearance by 47 %. This interaction is complicated by the fact that mean plasma AUC values of the N-desmethyl metabolite of topotecan, which is pharmacologically equipotent to that of topotecan, can be increased by 117 % [29].

Vincristine

Carbamazepine

Carbamazepine enhances the metabolism of vincristine, via an action on CYP3A4, and can increase mean plasma vincristine clearance values by 63 %, decrease mean plasma half-life values

	by 35 %, and decrease mean plasma vincristine AUC values by 43 % [30].
<i>Gabapentin</i>	Gabapentin does not affect the pharmacokinetics of vincristine [30].
<i>Oxcarbazepine</i>	Oxcarbazepine does not affect the pharmacokinetics of vincristine [30].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of vincristine, via an action on CYP3A4, and can increase mean plasma vincristine clearance values by 63 %, decrease mean plasma half-life values by 35 %, and decrease mean plasma vincristine AUC values by 43 % [30].
<i>Vigabatrin</i>	Vigabatrin does not affect the pharmacokinetics of vincristine [30].

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Antiulcer Drugs

Histamine H₂-Receptor Antagonists

Cimetidine

Gabapentin

Gabapentin does not affect the pharmacokinetics of cimetidine [1].

Phenobarbital

Phenobarbital decreases mean plasma cimetidine AUC values by 15 % [2].

Proton-Pump Inhibitors

Omeprazole

Carbamazepine

Carbamazepine enhances the metabolism of omeprazole, via an action on CYP3A4, and can decrease plasma omeprazole AUC values by 40 % [3].

Lacosamide

Lacosamide does not affect the pharmacokinetics of omeprazole [4].

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Cardiovascular Drugs

Antianginals

Ivabradine

- Carbamazepine*** Carbamazepine enhances the metabolism of ivabradine, via an action on CYP3A4, and can decrease mean plasma ivabradine C_{\max} and AUC values by 77 and 80 %, respectively [1].
- Phenytoin*** Phenytoin enhances the metabolism of ivabradine and can decrease mean plasma ivabradine C_{\max} and AUC values by 65 % and 69 % respectively [2].

Antiarrhythmics

Amiodarone

- Phenytoin*** Phenytoin enhances the metabolism of amiodarone and can decrease mean plasma amiodarone levels by 32–49 % [3].

*Disopyramide****Phenytoin***

Phenytoin enhances the metabolism of disopyramide and can decrease mean plasma disopyramide AUC values by 53 % and decrease mean plasma disopyramide elimination half-life values by 51 %. That there is a concurrent increase (up to 150 %) in the AUC values of the pharmacologically active metabolite (mono-*N*-dealkyldisopyramide) of disopyramide, complicates the interpretation of this interaction [4, 5].

*Mexiletine****Phenytoin***

Phenytoin enhances the metabolism of mexiletine and can decrease mean plasma mexiletine AUC values by 55 % and decrease mean plasma mexiletine elimination half-life values by 51 % [6].

*Quinidine****Phenobarbital***

Phenobarbital enhances the metabolism of quinidine, via an action on CYP3A4, and can decrease mean plasma quinidine elimination half-life values by 50 % and increase mean plasma quinidine clearance values by 60 % [7].

Phenytoin

Phenytoin enhances the metabolism of quinidine, via an action on CYP3A4, and can decrease mean plasma quinidine elimination half-life values by 50 % and increase mean plasma quinidine clearance values by 60 % [7].

Primidone Primidone enhances the metabolism of quinidine, via an action on CYP3A4, and can decrease plasma quinidine levels [7].

Antihypertensive Agents

Atenolol

Phenobarbital Phenobarbital can enhance the metabolism of atenolol and can decrease mean plasma AUC values by 24 % [8].

Diltiazem

Topiramate Topiramate can increase mean plasma diltiazem AUC values by 25 % [9].

Diazoxide

Phenytoin Phenytoin enhances the metabolism of diazoxide and can decrease plasma diazoxide levels [10].

Felodipine

Carbamazepine Carbamazepine enhances the metabolism of felodipine and can decrease mean plasma felodipine AUC values by 94 % and mean plasma felodipine levels by 82 % [11].

Phenobarbital Phenobarbital enhances the metabolism of felodipine and can decrease mean plasma felodipine AUC values by 94 % and mean plasma felodipine levels by 82 % [11].

Phenytoin Phenytoin enhances the metabolism of felodipine and can decrease mean plasma felodipine AUC values by 94 % and mean plasma felodipine levels by 82 % [11].

Oxcarbazepine Oxcarbazepine enhances the metabolism of felodipine and can decrease mean plasma felodipine C_{\max} values by 34 % and mean felodipine AUC values by 28 % [12].

Losartan

Phenytoin Phenytoin can increase mean plasma losartan AUC values by 17 % and can decrease mean plasma AUC values of the pharmacologically active carboxylic acid metabolite (E3174) of losartan by 63 %. The mechanism of the interaction is via an inhibition of CYP2C9-mediated conversion of losartan to E3174 [13].

Nifedipine

Phenobarbital Phenobarbital enhances the metabolism of nifedipine and can decrease plasma nifedipine AUC values by 60 % [14].

Phenytoin Phenytoin does not affect the pharmacokinetics of nifedipine [15].

Nilvadipine

Carbamazepine Carbamazepine enhances the metabolism of nilvadipine and can decrease plasma nilvadipine levels [16].

Nimodipine

Carbamazepine Carbamazepine enhances the metabolism of nimodipine and can decrease mean plasma nimodipine AUC values by 86 % [17].

Phenobarbital Phenobarbital enhances the metabolism of nimodipine and can decrease mean plasma nimodipine AUC values by 86 % [17].

Phenytoin Phenytoin enhances the metabolism of nimodipine and can decrease mean plasma nimodipine AUC values by 86 % [17].

Valproic Acid Valproic acid inhibits the metabolism of nimodipine and can increase mean plasma nimodipine AUC values by 54 % [17].

Nisoldipine

Phenytoin Phenytoin enhances the metabolism of nisoldipine and can decrease mean plasma nisoldipine AUC values by 90 % [18].

Propranolol

Phenobarbital Phenobarbital enhances the metabolism of propranolol and can decrease plasma propranolol levels [19].

Phenytoin Phenytoin enhances the metabolism of propranolol and can decrease plasma propranolol levels [19].

Topiramate Topiramate does not affect the pharmacokinetics of propranolol [20].

Verapamil

<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of verapamil and can increase mean verapamil plasma clearance by 4.3-fold and decrease mean plasma verapamil AUC values by 70 % [21].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of verapamil and can decrease plasma verapamil levels [22].

Digoxin

<i>Eslicarbazepine Acetate</i>	Eslicarbazepine acetate can decrease mean plasma digoxin C_{\max} values by 19 % and mean plasma digoxin AUC values by 8 % [23].
<i>Lacosamide</i>	Lacosamide does not affect the pharmacokinetics of digoxin [24].
<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of digoxin [25].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of digoxin and can decrease mean plasma digoxin half-life values by 30 %, decrease mean plasma digoxin AUC values by 23 %, and decrease plasma digoxin levels by 22 % [26].
<i>Tiagabine</i>	Tiagabine does not affect the pharmacokinetics of digoxin [27].
<i>Topiramate</i>	Topiramate can increase plasma digoxin clearance by 13 %, decrease plasma digoxin C_{\max} values by 16 %, and decrease plasma digoxin AUC values by 12 % [28].

Diuretics

Furosemide (Frusemide)

Phenytoin Phenytoin delays and reduces the magnitude of the diuretic effect of furosemide. It is thought that the mechanism of this interaction is a phenytoin-induced decrease in the spontaneous activity of gastrointestinal smooth muscle leading to reduced furosemide absorption [29].

Additionally, a pharmacodynamic interaction might occur since renal responsiveness to furosemide is also impaired [29].

Hydrochlorothiazide

Topiramate Topiramate does not affect the pharmacokinetics of hydrochlorothiazide [9].

Oral Anticoagulants

Dicoumarol

Phenytoin Phenytoin enhances the metabolism of dicoumarol, possibly via an action on CYP2C9, and can reduce the anticoagulant effects of dicoumarol [30].

Phenprocoumon

Carbamazepine Carbamazepine reduces the anticoagulant effects of phenprocoumon, possibly by increasing its metabolism [31].

Valproic Acid

Valproic acid does not affect the anticoagulant effect of phenprocoumon [31].

Warfarin**Carbamazepine**

Carbamazepine enhances the metabolism of warfarin resulting in a decrease in plasma warfarin half-life values, a decrease in plasma warfarin levels, and a decrease in the prothrombin time response to warfarin. Typically, a 2-fold increase in warfarin dosage is required so as to maintain an appropriate international normalized ratio (INR). Because enzyme induction may take several weeks to fully develop or subside, frequent monitoring of INR with appropriate dosage adjustment is advised for at least 4 weeks after starting or stopping carbamazepine [32, 33].

Upon carbamazepine discontinuation, warfarin levels will increase and may lead to potentially fatal hemorrhage [34].

Eslicarbazepine Acetate

Eslicarbazepine acetate has no effect on the pharmacokinetics of R-warfarin but decreases mean plasma S-warfarin C_{\max} and AUC values by 20 and 21 %, respectively. INR values are increased by 4 % but are not accompanied by a change in bleeding time [35].

Felbamate

Felbamate inhibits the metabolism of warfarin resulting in an increased INR [36].

- Levetiracetam** Levetiracetam does not affect the pharmacokinetics of warfarin [37].
- Oxcarbazepine** Oxcarbazepine does not affect the pharmacokinetics of warfarin [38].
- Phenobarbital** Phenobarbital enhances the metabolism of warfarin and decreases the prothrombin time response to warfarin. Typically, a 25–50 % increase in warfarin dosage is required. Because enzyme induction may take several weeks to fully develop or subside, frequent monitoring of INR with appropriate dosage adjustment is advised for at least 4 weeks after starting or stopping phenobarbital [39].
- Phenytoin** Despite an expected induction of warfarin metabolism by phenytoin, several cases of hypoprothrombinemia and severe bleeding complications have been reported after addition of phenytoin to warfarin. Proposed mechanisms for an enhanced anticoagulant response are displacement of warfarin from plasma protein binding sites or inhibition of its metabolism by phenytoin [40, 41].
- Because of potential induction and inhibition of warfarin metabolism via CYP 2C9 by phenytoin, the occurrence of a biphasic interaction has been suggested, with warfarin plasma levels initially increasing due to inhibition and then decreasing after 1–2 weeks as enzyme induction predominates. Thus, the interaction between phenytoin and warfarin is complex in that after an initial enhancement in anticoagulant

action, the latter can be subsequently decreased [42].

Due to the unpredictability of this interaction, frequent monitoring of INR with appropriate dosage adjustment is advised for at least 4 weeks after starting or stopping phenytoin.

Tiagabine

Tiagabine does not affect the pharmacokinetics of warfarin [43].

Valproic Acid:

Valproic acid can displace warfarin from its plasma protein binding sites, increase free pharmacologically active plasma warfarin levels, and lead to an increase in INR [44].

Statins

Atorvastatin

Lamotrigine

Lamotrigine increases mean plasma atorvastatin C_{\max} values by 14 % and mean plasma 2OH-atorvastatin and 4OH-atorvastatin (pharmacologically active metabolites) levels by 20 and 21 %, respectively. Inhibition through an effect on UGT1A1 and UGT1A3 is considered to be the mechanism of this interaction [45].

Phenytoin

Phenytoin decreases mean plasma atorvastatin C_{\max} values by 24 % and mean plasma 2OH-atorvastatin and 4OH-atorvastatin (pharmacologically active metabolites) levels by 22 and 52 %, respectively. Induction through an effect on CYP3A4 is considered to be the mechanism of this interaction [45].

Simvastatin

Carbamazepine

Carbamazepine enhances the metabolism of simvastatin, probably via an action on CYP3A4, and decreases mean plasma simvastatin and simvastatin acid AUC values by 75 and 82 %, respectively [46].

Eslicarbazepine Acetate

Eslicarbazepine acetate enhances the metabolism of simvastatin, probably via an action on CYP3A4, and decreases mean plasma simvastatin AUC values by 50 % [47]

Phenytoin

Phenytoin enhances the metabolism of simvastatin, probably via an action on CYP3A4, and decreases plasma simvastatin levels [48].

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Immunosuppressants

Cyclosporine A

<i>Acetazolamide</i>	Acetazolamide can increase plasma cyclosporine level [1].
<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of cyclosporine, via an action on CYP3A4, and can decrease plasma cyclosporine levels by >75 % [2, 3].
<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of cyclosporine [4].
<i>Oxcarbazepine</i>	Oxcarbazepine can decrease plasma cyclosporine levels by up to 25 % [5].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of cyclosporine, via an action on CYP3A4, and can decrease plasma cyclosporine levels by up to 95 % [6].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of cyclosporine, via an action on CYP3A4, and can decrease mean plasma cyclosporine and mean whole blood cyclosporine AUC values by 47 and 44 %, respectively [7].
<i>Primidone</i>	Primidone enhances the metabolism of cyclosporine, via an action on CYP3A4, and can decrease plasma cyclosporine levels [8].

Valproic Acid Valproic acid does not affect the pharmacokinetics of cyclosporine. However, its use, particularly in renal transplant recipients, should be weighed out against possible risks of hepatotoxicity consequent to its pharmacologically active metabolite(s) [2].

Sirolimus

Phenytoin Phenytoin enhances the metabolism of sirolimus, via an action on CYP3A4/5, and can decrease plasma sirolimus levels by 74 % [9].

Tacrolimus

Carbamazepine Carbamazepine enhances the metabolism of tacrolimus, via induction of CYP3A, and can decrease plasma tacrolimus levels [10].

Levetiracetam Levetiracetam does not affect the pharmacokinetics of tacrolimus [11].

Phenytoin Phenytoin enhances the metabolism of tacrolimus, via induction of CYP3A, and can decrease plasma tacrolimus levels [12].

Phenobarbital Phenobarbital enhances the metabolism of tacrolimus, via induction of CYP3A, and can decrease plasma tacrolimus levels [11].

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Neuromuscular Blocking Agents

Atracurium

Carbamazepine

Carbamazepine has been reported not to affect the pharmacokinetics of atracurium and also to enhance the metabolism of atracurium resulting in decreased duration of neuromuscular blockade and higher doxacurium dosage requirements [1, 2].

Phenytoin

Phenytoin has been reported not to affect the pharmacokinetics of atracurium and also to enhance the metabolism of atracurium resulting in decreased duration of neuromuscular blockade and higher doxacurium dosage requirements [1, 3].

Cisatracurium

Carbamazepine

Carbamazepine enhances the metabolism of cisatracurium and can increase plasma cisatracurium clearance by 25 %. Patients receiving chronic

therapy with carbamazepine show a decreased duration of neuromuscular blockade and higher cisatracurium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [4].

Phenytoin

Phenytoin enhances the metabolism of cisatracurium and can increase plasma cisatracurium clearance by 25 %.

Patients receiving chronic therapy with phenytoin show a decreased duration of neuromuscular blockade and higher cisatracurium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [4].

Doxacurium

Carbamazepine

Carbamazepine enhances the metabolism of doxacurium. Patients receiving chronic therapy with carbamazepine show a decreased duration of neuromuscular blockade and higher doxacurium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [5].

Phenytoin

Phenytoin enhances the metabolism of doxacurium. Patients receiving chronic therapy with phenytoin show a decreased duration of neuromuscular blockade and higher doxacurium

dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [5].

Mivacurium

Carbamazepine

Carbamazepine does not affect the pharmacokinetics of mivacurium [6].

Phenytoin

Phenytoin does not affect the pharmacokinetics of mivacurium [7].

Valproic Acid

Valproic acid does not affect the pharmacokinetics of mivacurium [7].

Pancuronium

Carbamazepine

Carbamazepine enhances the metabolism of pancuronium. Patients receiving chronic therapy with carbamazepine show a decreased duration of neuromuscular blockade and higher pancuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [8].

Phenytoin

Phenytoin enhances the metabolism of pancuronium. Patients receiving chronic therapy with phenytoin show a decreased duration of neuromuscular blockade and higher pancuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [9].

Pipecuronium

Carbamazepine

Carbamazepine enhances the metabolism of pipecuronium. Patients receiving chronic therapy with carbamazepine show a decreased duration of neuromuscular blockade and higher pancuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [10].

Rapacuronium

Carbamazepine

Carbamazepine enhances the metabolism of rapacuronium. Patients receiving chronic therapy with carbamazepine show a decreased duration of neuromuscular blockade and higher rapacuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [11].

Phenytoin

Phenytoin enhances the metabolism of rapacuronium. Patients receiving chronic therapy with phenytoin show a decreased duration of neuromuscular blockade and higher rapacuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [11].

Rocuronium

Carbamazepine

Carbamazepine enhances the metabolism of rocuronium. Patients receiving chronic therapy with carbamazepine show a decreased duration of neuromuscular blockade and higher rocuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [12].

Phenytoin

Phenytoin does not affect the pharmacokinetics of rocuronium when administered acutely and instead results in a potentiation of neuromuscular block. However, when administered chronically, phenytoin enhances the metabolism of rocuronium. Patients receiving chronic therapy with phenytoin show a decreased duration of neuromuscular blockade and higher rocuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [13, 14].

Primidone

Primidone enhances the metabolism of rocuronium. Patients receiving chronic therapy with primidone show a decreased duration of neuromuscular blockade and higher rocuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [15].

Valproic Acid Valproic acid probably does not affect the pharmacokinetics of rocuronium [15].

Vecuronium

Carbamazepine Carbamazepine enhances the metabolism of vecuronium and can decrease plasma vecuronium half-life values by 62 % and can increase vecuronium clearance values by 2-fold. Patients receiving chronic therapy with carbamazepine show a decreased duration of neuromuscular blockade and higher vecuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [16].

Phenytoin Phenytoin does not affect the pharmacokinetics of vecuronium when administered acutely and instead can result in a potentiation of neuromuscular block. However, when administered chronically, phenytoin enhances the metabolism of vecuronium and can decrease plasma vecuronium half-life values by 51 % and can increase plasma vecuronium clearance values by 68 %. Patients receiving chronic therapy with phenytoin show a decreased duration of neuromuscular blockade and higher vecuronium dosage requirements. Both pharmacokinetic (enzyme induction) and pharmacodynamic (upregulation of acetylcholine receptors) mechanisms may explain this interaction [17, 18].

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Psychotropic Drugs

Antidepressants

Amitriptyline

Carbamazepine

Carbamazepine enhances the metabolism of amitriptyline and can decrease mean plasma amitriptyline levels by 59 % [1].

Topiramate

Topiramate enhances the metabolism of amitriptyline and can increase mean plasma amitriptyline clearance by 8 % and increase mean plasma amitriptyline and nortriptyline (the pharmacologically active metabolite of amitriptyline) AUC values by 8 and 19 %, respectively. Mean steady-state amitriptyline levels can decrease by 23–33 % [2].

Valproic Acid

Valproic acid inhibits the metabolism of amitriptyline and can increase mean plasma amitriptyline AUC values by 30 % and mean plasma amitriptyline levels by 19 %. The corresponding values for nortriptyline are 55 and 28 %, respectively [3].

Citalopram

Carbamazepine Carbamazepine enhances the metabolism of citalopram, probably via an action on CYP3A4, and can decrease mean plasma citalopram levels by 27–31 % [4].

Oxcarbazepine Oxcarbazepine does not affect the pharmacokinetics of citalopram [5].

Clomipramine

Carbamazepine Carbamazepine inhibits the metabolism of clomipramine and can increase plasma clomipramine levels [6].

Valproic Acid Valproic acid inhibits the metabolism of clomipramine and can increase plasma clomipramine levels [7, 8].

Desipramine

Carbamazepine Carbamazepine enhances the metabolism of desipramine and can increase mean plasma desipramine clearance values by 31 % and decreases mean plasma desipramine half-life values by 20 % and can decrease plasma desipramine levels [9].

Phenobarbital Phenobarbital enhances the metabolism of desipramine and can decrease mean plasma desipramine levels by 31 % [10].

Phenytoin Phenytoin enhances the metabolism of desipramine and can decrease plasma desipramine levels [11].

Doxepin

Carbamazepine Carbamazepine enhances the metabolism of doxepin and can decrease mean plasma doxepin levels by 55 % [1].

Fluoxetine

Carbamazepine It is not known whether carbamazepine affects the pharmacokinetics of fluoxetine.

A pharmacodynamic interaction (toxic serotonin syndrome) can occur between the two drugs [12].

Imipramine

Carbamazepine Carbamazepine enhances the metabolism of imipramine and can decrease plasma imipramine levels by 42 % [13].

Phenobarbital Phenobarbital enhances the metabolism of imipramine and can decrease plasma imipramine levels [14].

Mianserin

Carbamazepine Carbamazepine enhances the metabolism of mianserin, via an action on CYP3A4, and can decrease plasma mianserin (unconjugated and total (S)-mianserin – the more potent enantiomer) levels by 56 % [15].

Phenobarbital Phenobarbital enhances the metabolism of mianserin and can decrease plasma mianserin levels [16, 17].

Phenytoin Phenytoin enhances the metabolism of mianserin and can decrease plasma mianserin levels [16, 17].

Mirtazapine

Carbamazepine Carbamazepine enhances the metabolism of mirtazapine and can increase mean plasma mirtazapine clearance values by 137 % and can decrease mean plasma mirtazapine AUC values by 61 % [18].

Phenytoin Phenytoin enhances the metabolism of mirtazapine and can decrease mean plasma mirtazapine AUC values by 47 % and mean plasma mirtazapine levels by 33 % [19].

Moclobemide

Carbamazepine Carbamazepine enhances the metabolism of moclobemide, probably via an action on CYP2C19, and can increase mean plasma moclobemide clearance values by 1.4-fold and decrease mean plasma moclobemide AUC values by 36 % and mean plasma moclobemide levels by 52 % [20].

Valproic Acid Valproic acid can increase mean plasma moclobemide clearance values by 6 % and decrease mean plasma moclobemide AUC values by 11 % and mean plasma moclobemide levels by 19 % [20].

Nefazodone

Carbamazepine Carbamazepine enhances the metabolism of nefazodone and can decrease mean plasma AUC values by 92 % [21].

Nortriptyline

Carbamazepine Carbamazepine enhances the metabolism of nortriptyline and can decrease plasma nortriptyline levels by 62 % [22].

Phenobarbital Phenobarbital enhances the metabolism of nortriptyline and can decrease plasma nortriptyline levels [23].

Phenytoin Phenytoin enhances the metabolism of nortriptyline and can decrease plasma nortriptyline levels [23].

Primidone Primidone enhances the metabolism of nortriptyline and can decrease plasma nortriptyline levels [23].

Valproic Acid Valproic acid inhibits the metabolism of nortriptyline and can increase plasma nortriptyline levels [24].

Paroxetine

Phenobarbital Phenobarbital enhances the metabolism of paroxetine and can decrease mean plasma paroxetine levels by 25 % [25].

Phenytoin Phenytoin enhances the metabolism of paroxetine and can decrease plasma paroxetine levels [26].

Sertraline

- Carbamazepine*** Carbamazepine enhances the metabolism of sertraline and can decrease plasma sertraline levels. However, plasma levels of its metabolite, desmethylsertraline, are increased concurrently [27, 28].
- Phenytoin*** Phenytoin enhances the metabolism of sertraline and can decrease plasma sertraline levels [28].

Venlafaxine

- Topiramate*** Topiramate does not affect the pharmacokinetics of venlafaxine [29].

Viloxazine

- Carbamazepine*** Carbamazepine does not affect the pharmacokinetics of viloxazine [30].
- Phenobarbital*** Phenobarbital does not affect the pharmacokinetics of viloxazine [30].
- Phenytoin*** Phenytoin does not affect the pharmacokinetics of viloxazine [30].

Antipsychotics

Amisulpride

- Carbamazepine*** It is not known whether carbamazepine affects the pharmacokinetics of amisulpride.
- A pharmacodynamic interaction between carbamazepine and amisulpride has been suggested [31].

Oxcarbazepine

It is not known whether oxcarbazepine affects the pharmacokinetics of amisulpride.

A pharmacodynamic interaction between oxcarbazepine and amisulpride has been suggested [32].

Aripiprazole***Carbamazepine***

Carbamazepine can decrease mean plasma aripiprazole C_{\max} and AUC values by 66 and 71 %, respectively, while values of its pharmacologically active metabolite, dehydroaripiprazole, are decreased by 68 and 69 %, respectively. The mechanism of this interaction is considered to be induction of aripiprazole metabolism, mediated via CYP3A4, and induction of dehydroaripiprazole metabolism also mediated via CYP3A4 [33].

A pharmacodynamic interaction between carbamazepine and aripiprazole has also been suggested [34].

Clonazepam

Clonazepam does not affect the pharmacokinetics of aripiprazole [35].

Lamotrigine

Lamotrigine inhibits the metabolism of aripiprazole to its pharmacologically active metabolite dehydroaripiprazole so that the plasma dehydroaripiprazole/aripiprazole ratio decreases by 17 % [35].

Valproic Acid

Valproic can decrease mean plasma aripiprazole C_{\max} and AUC values by 25 and 24 %, respectively, while values for its pharmacologically active metabolite, dehydroaripiprazole, are only decreased by 8 and 7 %, respectively.

The mechanism of this interaction is considered to be by either induction of aripiprazole metabolism, mediated via CYP3A4 and CYP2D6, or by displacement of aripiprazole from its protein binding sites by valproic acid [36].

Asenapine

Valproic Acid

Valproic acid does not affect the pharmacokinetics of asenapine [37].

Bromperidol

Carbamazepine

Carbamazepine enhances the metabolism of bromperidol and can decrease mean plasma bromperidol levels by 37 % [38].

Clozapine

Carbamazepine

Carbamazepine enhances the metabolism of clozapine and can decrease plasma clozapine levels by 31–63 % [39].

Combining carbamazepine with clozapine is generally contraindicated due to concerns about potential additive adverse hematological effects [40].

Lamotrigine

Lamotrigine does not affect the pharmacokinetics of clozapine [41, 42].

Oxcarbazepine

In a comparison of the effect of carbamazepine and oxcarbazepine on plasma clozapine levels, mean clozapine levels were 47 % lower with carbamazepine compared to oxcarbazepine [43].

<i>Phenytoin</i>	Phenytoin enhances the metabolism of clozapine and can decrease plasma clozapine levels by 75–84 % [44].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of clozapine, via the enhancement of N-oxidation and demethylation pathways, and can decrease mean plasma clozapine levels by 35 % [45].
<i>Topiramate</i>	Topiramate does not affect the pharmacokinetics of clozapine [46].
<i>Valproic Acid</i>	There are conflicting reports on the potential effects of valproic acid on plasma clozapine levels. One study observed a 57 % increase in plasma clozapine levels with the addition of valproic acid, while a second study found a 15 % decrease. A third study reported an 11 % increase in plasma clozapine levels via an action on CYP1A2 and CYP3A4. All studies observed a decrease in plasma levels of norclozapine, the pharmacologically active metabolite of clozapine [47, 48].

Chlorpromazine

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of chlorpromazine and can decrease plasma chlorpromazine levels [49].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of chlorpromazine and can decrease plasma chlorpromazine levels by ~25 % [50].

Fluphenazine

Carbamazepine Carbamazepine enhances the metabolism of fluphenazine and can decrease plasma fluphenazine levels by 49 % [51].

Haloperidol

Carbamazepine Carbamazepine enhances the metabolism of haloperidol and can decrease plasma haloperidol levels by 59–61 % [52].

Phenobarbital Phenobarbital enhances the metabolism of haloperidol and can decrease plasma haloperidol levels by 50–60 % [53].

Phenytoin Phenytoin enhances the metabolism of haloperidol and can decrease plasma haloperidol levels by 50–60 % [53].

Topiramate Topiramate can increase plasma haloperidol AUC values by up to 28 %. The AUC values of the pharmacologically active metabolite of haloperidol are concurrently increased by up to 50 % [54].

Valproic Acid Valproic acid does not affect the pharmacokinetics of haloperidol [55].

Olanzapine

Carbamazepine Carbamazepine enhances the metabolism of olanzapine, via an action on glucuronidation, and can increase mean plasma olanzapine clearance values by 46 % and can decrease mean plasma olanzapine AUC values by 44 % [56].

<i>Lamotrigine</i>	Lamotrigine can increase mean plasma olanzapine levels by 16 %. The interaction is considered to be the consequence of inhibition of UGT1A4-mediated olanzapine glucuronidation [42].
<i>Oxcarbazepine</i>	Oxcarbazepine does not affect the pharmacokinetics of olanzapine [57].
<i>Rufinamide</i>	Rufinamide does not affect the pharmacokinetics of olanzapine [58].
<i>Topiramate</i>	Topiramate does not affect the pharmacokinetics of olanzapine [46].
<i>Valproic Acid</i>	Valproic acid can decrease mean plasma olanzapine levels by 18 % [59].

Quetiapine

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of quetiapine, via an action on CYP3A4, and can increase plasma quetiapine clearance by 7.5-fold and decrease mean plasma quetiapine C_{\max} values by 80 % or to undetectable levels [60, 61].
<i>Lamotrigine</i>	Lamotrigine enhances the metabolism of quetiapine and decreases quetiapine plasma levels [62].
<i>Oxcarbazepine</i>	Oxcarbazepine does not affect the pharmacokinetics of quetiapine [63].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of quetiapine, probably via an action on CYP3A4, and can increase plasma quetiapine clearance by 5-fold and can decrease mean plasma quetiapine C_{\max} and AUC values by 27 and 19 %, respectively [64].

<i>Topiramate</i>	Topiramate does not affect the pharmacokinetics of quetiapine [46].
<i>Valproic Acid</i>	Valproic acid inhibits the metabolism of quetiapine, probably via an action on CYP3A4, and can increase plasma quetiapine levels by 77 % [65].

Risperidone

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of risperidone and its pharmacologically active metabolite 9-hydroxyrisperidone, probably via an action on CYP3A4, and can decrease mean plasma risperidone and 9-hydroxyrisperidone levels by 68 and 64 %, respectively [66].
<i>Lamotrigine</i>	Lamotrigine does not affect the pharmacokinetics of risperidone [42].
<i>Oxcarbazepine</i>	Oxcarbazepine does not affect the pharmacokinetics of risperidone [57].
<i>Phenytoin</i>	Phenytoin inhibits the metabolism of risperidone and can increase plasma risperidone levels [67].
<i>Topiramate</i>	Topiramate can increase mean risperidone clearance values by 51 % and decrease mean plasma risperidone AUC values by 23 %. Mean plasma 9-hydroxyrisperidone (the pharmacologically active metabolite of risperidone) AUC values are concurrently decreased by 8 % [2].
<i>Valproic Acid</i>	Valproic acid does not affect the pharmacokinetics of risperidone [66, 68].

*Thioridazine****Carbamazepine***

Carbamazepine does not affect the plasma levels of thioridazine but decreases plasma levels of the pharmacologically active metabolite, mesoridazine [43].

Phenobarbital

Phenobarbital enhances the metabolism of thioridazine and can decrease plasma thioridazine levels by 10 %. However, phenobarbital also enhances the metabolism of the pharmacologically active metabolite, mesoridazine, and can decrease plasma mesoridazine levels by 25 % [53].

Phenytoin

Phenytoin enhances the metabolism of thioridazine and can decrease plasma thioridazine levels by 10 %. However, phenytoin also enhances the metabolism of the pharmacologically active metabolite of thioridazine (mesoridazine) and can decrease plasma mesoridazine levels by 25 % [53].

*Trazodone****Carbamazepine***

Carbamazepine enhances the metabolism of trazodone and can decrease mean plasma trazodone levels by 24 % and decrease mean plasma m-chlorophenylpiperazine levels, the pharmacologically active metabolite, by 40 % [69].

Ziprasidone

Carbamazepine Carbamazepine enhances the metabolism of ziprasidone, probably via an action on CYP3A4, and can decrease mean plasma ziprasidone AUC values by 36 % and mean plasma ziprasidone levels by 27 % [70].

Benzodiazepines*Alprazolam*

Carbamazepine Carbamazepine enhances the metabolism of alprazolam, probably via an action on CYP3A4, and can increase mean plasma alprazolam clearance values by 137 % and decrease mean plasma alprazolam half-life values by 55 %. Mean plasma alprazolam levels are decreased by >50 % [71, 72].

Clobazam

Carbamazepine Carbamazepine enhances the metabolism of clobazam. Plasma levels of the pharmacologically active metabolite of clobazam, *N*-desmethyloclobazam, are increased during co-medication with carbamazepine. The mean plasma *N*-desmethyloclobazam/clobazam ratio is increased by 117 % [73].

Eslicarbazepine Acetate Eslicarbazepine acetate does not affect the pharmacokinetics of clobazam [74].

Felbamate Felbamate inhibits the metabolism of clobazam. Plasma levels of the

	pharmacologically active metabolite of clobazam, <i>N</i> -desmethyloclobazam, are increased during co-medication with felbamate. Typically, the plasma level to weight-adjusted dose ratio of <i>N</i> -desmethyloclobazam and clobazam can be expected to be 5-fold lower and 2-fold higher, respectively. The interaction may be the consequence of inhibition of <i>N</i> -desmethyloclobazam metabolism through CYP2C19 [75].
<i>Lamotrigine</i>	Lamotrigine does not affect the pharmacokinetics of clobazam [73].
<i>Levetiracetam</i>	Levetiracetam does not affect the pharmacokinetics of clobazam [76].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of clobazam. Plasma levels of the pharmacologically active metabolite of clobazam, <i>N</i> -desmethyloclobazam, are increased during co-medication with phenobarbital. The mean plasma <i>N</i> -desmethyloclobazam/clobazam ratio is increased by 90 % [73].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of clobazam. Plasma levels of the pharmacologically active metabolite of clobazam, <i>N</i> -desmethyloclobazam, are increased during co-medication with phenytoin. The mean plasma <i>N</i> -desmethyloclobazam/clobazam ratio is increased by 294 % [73].
<i>Rufinamide</i>	Rufinamide does not affect the pharmacokinetics of clobazam [77].
<i>Stiripentol</i>	Stiripentol inhibits the metabolism of clobazam. Plasma levels of clobazam and the pharmacologically active metabolite of clobazam, <i>N</i> -desmethyloclobazam, are increased during co-medication with stiripentol.

Typically, the plasma levels of clobazam and *N*-desmethyloclobazam can be expected to be 2-fold higher and 3-fold higher, respectively. The interaction is the consequence of inhibition of *N*-demethylation of clobazam through CYP3A4 and the inhibition of the hydroxylation of *N*-desmethyloclobazam by CYP2C19 [78].

Valproic Acid

Valproic acid does not affect the pharmacokinetics of clobazam [73].

Clonazepam

Carbamazepine

Carbamazepine enhances the metabolism of clonazepam and can decrease plasma clonazepam levels by 19–37 % [79].

Felbamate

Felbamate inhibits the metabolism of clonazepam. Mean plasma clonazepam levels and AUC values can be increased by 17 and 24 %, respectively [80].

Lacosamide

Lacosamide does not affect the pharmacokinetics of clonazepam [81].

Lamotrigine

Lamotrigine enhances the metabolism of clonazepam and can decrease plasma clonazepam levels by 20–38 % [82].

Levetiracetam

Levetiracetam does not affect the pharmacokinetics of clonazepam [76].

Phenobarbital

Phenobarbital enhances the metabolism of clonazepam. Mean plasma clonazepam clearance can be increased by 19–24 %, and mean plasma clonazepam levels can be decreased by 11 % [83].

Phenytoin

Phenytoin enhances the metabolism of clonazepam. Mean plasma clonazepam clearance can be increased by 46–58 %, and mean plasma clonazepam levels can be decreased by 28 % [83].

Primidone Primidone enhances the metabolism of clonazepam and can decrease plasma clonazepam levels [84].

Diazepam

Carbamazepine Carbamazepine enhances the metabolism of diazepam so that mean plasma diazepam half-life values are decreased by 62 % and mean plasma diazepam clearance values are increased by 158 %. A concurrent increase in plasma *N*-desmethyldiazepam, the pharmacologically active metabolite of diazepam, levels also occurs [85].

Phenobarbital Phenobarbital enhances the metabolism of diazepam so that mean plasma diazepam half-life values are decreased by 62 % and mean plasma diazepam clearance values are increased by 158 %. A concurrent increase in plasma *N*-desmethyldiazepam, the pharmacologically active metabolite of diazepam, levels also occurs [85].

Phenytoin Phenytoin enhances the metabolism of diazepam so that mean plasma diazepam half-life values are decreased by 62 % and mean plasma diazepam clearance values are increased by 158 %. A concurrent increase in plasma *N*-desmethyldiazepam, the pharmacologically active metabolite of diazepam, levels also occurs [85].

Primidone Primidone enhances the metabolism of diazepam so that mean plasma diazepam half-life values are decreased by 62 % and mean plasma diazepam clearance values are increased by 158 %. A concurrent increase in plasma

N-desmethyldiazepam, the pharmacologically active metabolite of diazepam, levels also occurs [84].

Valproic Acid

Valproic acid displaces diazepam from its plasma protein binding (albumin) sites so that mean free plasma diazepam levels are increased by 92 % [86].

Lorazepam

Pregabalin

Pregabalin does not affect the pharmacokinetics of lorazepam.

However, during combination therapy, impairment of cognitive and gross motor functions is observed, and these are considered to be the consequence of a pharmacodynamic interaction [87].

Valproic Acid

Valproic acid can decrease the mean plasma clearance of lorazepam by 31 % and increase mean plasma lorazepam levels by 31 % [88].

Midazolam

Carbamazepine

Carbamazepine enhances the metabolism of midazolam and can decrease plasma midazolam levels. Because the mean decrease in plasma midazolam AUC values of orally administered midazolam in patients taking carbamazepine is so marked (94 %), the loss of efficacy of the hypnotic can be readily anticipated. However, since midazolam clearance after intravenous administration is more dependent on liver blood

flow than on enzyme activity, this interaction would be expected to be far less important when midazolam is given parenterally [89].

Phenytoin

Phenytoin enhances the metabolism of midazolam and can decrease plasma midazolam levels. Because the mean decrease in plasma midazolam AUC values of orally administered midazolam in patients taking phenytoin is so marked (94 %), the loss of efficacy of the hypnotic can be readily anticipated. However, since midazolam clearance after intravenous administration is more dependent on liver blood flow than on enzyme activity, this interaction would be expected to be far less important when midazolam is given parenterally [89].

Lithium

Acetazolamide

Acetazolamide can increase plasma lithium levels by 5-fold. This may be the consequence of carbonic anhydrase inhibition by acetazolamide resulting in a decrease in lithium renal clearance [90].

Carbamazepine

Carbamazepine can increase plasma lithium levels by 3.5-fold resulting in lithium toxicity consequent to carbamazepine-induced acute renal failure [91].

A pharmacodynamic interaction between lithium and carbamazepine has been described whereby patients develop a syndrome characterized by somnolence, confusion, disorientation, and ataxia and other cerebella symptoms [92, 93].

<i>Clonazepam</i>	Clonazepam can increase plasma lithium levels by 33–61 % [94].
<i>Gabapentin</i>	Gabapentin does not affect the pharmacokinetics of lithium [95].
<i>Lamotrigine</i>	Lamotrigine can decrease mean plasma lithium AUC values by 8 % [96].
<i>Topiramate</i>	The effects of topiramate in the pharmacokinetics of lithium are controversial. Topiramate has been reported to increase mean plasma lithium clearance by 36 % and to decrease mean plasma lithium AUC values by 12 %. Topiramate has also been reported to increase plasma lithium levels by up to 140 %. Both these effects are considered to be the consequence of carbonic anhydrase inhibition by topiramate which in turn affects lithium renal clearance [2, 97].
<i>Valproic Acid</i>	Valproic acid does not affect the pharmacokinetics of lithium [98].

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Steroids

Corticosteroids

Cortisol/Hydrocortisone

<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of cortisol and can decrease plasma cortisol levels [1].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of cortisol and can decrease mean plasma cortisol half-life values by 37 % [2].

Dexamethasone

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of dexamethasone and can increase plasma dexamethasone clearance [3].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of dexamethasone and can increase plasma dexamethasone clearance [4].
<i>Phenytoin</i>	Phenytoin decreases mean dexamethasone half-life values by 46 % and increases mean plasma dexamethasone clearance values by 190 % [5].

Primidone Primidone enhances the metabolism of dexamethasone and can decrease plasma dexamethasone levels [6].

Methylprednisolone

Carbamazepine Carbamazepine enhances the metabolism of methylprednisolone and can increase mean plasma methylprednisolone clearance by 342 % [7].

Phenobarbital Phenobarbital enhances the metabolism of methylprednisolone and can increase mean plasma methylprednisolone clearance by 209 % [7].

Phenytoin Phenytoin enhances the metabolism of methylprednisolone and can increase mean plasma methylprednisolone clearance by 479 % [7].

Prednisolone

Carbamazepine Carbamazepine enhances the metabolism of prednisolone and can decrease mean plasma prednisolone half-life values by 28 % and can increase mean plasma prednisolone clearance by 42 % [8].

Phenobarbital Phenobarbital enhances the metabolism of prednisolone and can increase mean plasma prednisolone clearance by 41 % [7].

Phenytoin Phenytoin enhances the metabolism of prednisolone and can decrease mean plasma prednisolone half-life values by 45 % and can increase mean plasma prednisolone clearance by 77 % [9].

Oral Contraceptives

<i>Acetazolamide</i>	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. This loss of effectiveness relates to enhancement of the metabolism of the ethinylestradiol and levonorgestrel components of oral contraceptives. Typically, mean plasma ethinylestradiol AUC values can decrease by ~45 %, and mean plasma levonorgestrel AUC values can decrease by ~44 % [10].
<i>Clobazam</i>	The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.
<i>Clonazepam</i>	Clonazepam does not affect the metabolism of oral contraceptives [11].
<i>Eslicarbazepine Acetate</i>	Eslicarbazepine acetate enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. This loss of effectiveness relates to enhancement of the metabolism of the ethinylestradiol and levonorgestrel components of oral contraceptives. Typically, plasma ethinylestradiol AUC values can decrease by ~32 %, and plasma levonorgestrel AUC values can decrease by ~13 % [12].
<i>Ethosuximide</i>	Ethosuximide does not affect the metabolism of oral contraceptives [13].

Felbamate

Felbamate enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. Typically, plasma gestodene (progestin) AUC values can decrease by 42 %, and plasma ethinylestradiol AUC values can decrease by 13 % [14].

Gabapentin

Gabapentin does not affect the metabolism of oral contraceptives [15].

Lacosamide

Lacosamide does not affect the metabolism of oral contraceptives [16].

Lamotrigine

Lamotrigine does not affect the metabolism of oral contraceptives.

The interaction between lamotrigine and oral contraceptives has been extensively studied, and while lamotrigine does not affect the estrogen component of the oral contraceptives pill, it produces a modest 12 % reduction in the progesterone level which, although probably of no clinical significance in most patients, this may result in contraceptive failure in some patients – particularly if they are prescribed the progesterone-only pill [17].

Levetiracetam

Levetiracetam does not affect the metabolism of oral contraceptives [18].

Oxcarbazepine

Oxcarbazepine enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. This loss of effectiveness relates to induction of the metabolism of the ethinylestradiol and levonorgestrel components of oral contraceptives. Typically, mean plasma ethinylestradiol AUC values can decrease by 47 %, and mean plasma levonorgestrel AUC

values can decrease by 47 %, possibly due to induction of UGT1A4 by estrogen [19].

Phenobarbital

Phenobarbital enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. This loss of effectiveness relates to induction of the CYP3A4-mediated metabolism of ethinylestradiol and levonorgestrel. Typically, plasma ethinylestradiol and levonorgestrel AUC values can decrease by 40 % [20].

Phenytoin

Phenytoin enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. This loss of effectiveness relates to induction of the CYP3A4-mediated metabolism of ethinylestradiol and levonorgestrel. Typically, plasma ethinylestradiol and levonorgestrel AUC values can decrease by 50 % [21].

Piracetam

The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

Pregabalin

Pregabalin does not affect the metabolism of oral contraceptives [22].

Primidone

Primidone enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. This loss of effectiveness relates to induction of the CYP3A4-mediated metabolism of ethinylestradiol and levonorgestrel. Typically, plasma ethinylestradiol and levonorgestrel AUC values can decrease by 40 % [20].

<i>Retigabine</i>	Retigabine does not affect the metabolism of oral contraceptives [23].
<i>Rufinamide</i>	Rufinamide enhances the metabolism of oral contraceptives, thereby reducing the efficacy of the contraceptive pill and causing contraceptive failure. This loss of effectiveness relates to induction of the CYP3A4 and/or UGT-mediated metabolism of ethinylestradiol and levonorgestrel. Typically, plasma ethinylestradiol and norethindrone levels are decreased by 22 and 14 %, respectively [24].
<i>Stiripentol</i>	It is not known whether stiripentol affects hormonal contraception, but theoretically, it can increase plasma levels of hormonal contraceptives and thus necessitate lower doses to be prescribed.
<i>Sulthiame</i>	It is not known whether sulthiame affects hormonal contraception, but theoretically, it can increase plasma levels of hormonal contraceptives and thus necessitate lower doses to be prescribed.
<i>Tiagabine</i>	Tiagabine does not affect the metabolism of oral contraceptives [25].
<i>Topiramate</i>	Topiramate caused a dose-dependent decrease in mean plasma ethinylestradiol AUC values (200 mg – 18 %; 400 mg – 21 %; 800 mg – 30 %) but no change in plasma norethindrone levels. The interaction is minimal (mean plasma ethinylestradiol AUC values decrease by 12 %) or absent at topiramate daily dosages of 100 mg or less. Nevertheless, because contraceptive effectiveness may be affected, caution is

	advised in patients receiving topiramate and oral contraceptives [26, 27].
Valproic Acid	Valproic acid does not affect the metabolism of oral contraceptives [28].
Vigabatrin	Vigabatrin does not affect the metabolism of oral contraceptives [29].
Zonisamide	Zonisamide does not affect the metabolism of oral contraceptives [30].

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Miscellanea

Bupropion

Carbamazepine Carbamazepine enhances the metabolism of bupropion and can decrease mean plasma bupropion AUC values by 90 % and can increase mean plasma hydroxybupropion, the pharmacologically active metabolite of bupropion, values by 50 % [1].

Valproic Acid Valproic acid does not affect the metabolism of bupropion, but it can increase mean plasma hydroxybupropion, the pharmacologically active metabolite of bupropion, values by 94 % [1].

Dextromethorphan

Clobazam Clobazam inhibits the metabolism of dextromethorphan and can increase mean plasma dextromethorphan AUC values by 60 % [2].

Dihydroergotamine

Topiramate Topiramate does not affect the pharmacokinetics of dihydroergotamine [3].

Fexofenadine

Carbamazepine Carbamazepine decreases mean plasma fexofenadine C_{\max} values by 42 % and mean plasma fexofenadine AUC values by 43 %. The mechanism of this interaction is considered to be induction of P-glycoprotein in the small intestine [4].

Flunarizine

Topiramate Topiramate does not affect the pharmacokinetics of flunarizine [5].

Glibenclamide (Glyburide)

Topiramate Topiramate decreases mean plasma glibenclamide AUC values by 25 % and decreases mean plasma AUC values of its two pharmacologically active metabolites (4-trans-hydroxy-glibenclamide and 3-cis-hydroxy-glibenclamide) by 13 and 15 %, respectively [5].

Isoxicam

Phenytoin Phenytoin increases the rate and extent of absorption of isoxicam and increases mean plasma isoxicam values by 19 % [6].

Lidocaine (Lignocaine)

<i>Carbamazepine</i>	Carbamazepine enhances the metabolism of lidocaine, probably via an action on CYP3A4, and can increase mean plasma lidocaine clearance by 196 % and can decrease mean plasma lidocaine AUC values by 60 % [7].
<i>Phenobarbital</i>	Phenobarbital enhances the metabolism of lidocaine, probably via an action on CYP3A4, and can increase mean plasma lidocaine clearance values by 196 % and can decrease mean plasma lidocaine AUC values by 60 % [7].
<i>Phenytoin</i>	Phenytoin enhances the metabolism of lidocaine, probably via an action on CYP3A4, and can increase mean plasma lidocaine clearance values by 196 % and can decrease mean plasma lidocaine AUC values by 60 % [7].
<i>Primidone</i>	Primidone enhances the metabolism of lidocaine, probably via an action on CYP3A4, and can increase mean plasma lidocaine clearance values by 196 % and can decrease mean plasma lidocaine AUC values by 60 % [7].

Metformin

<i>Eslicarbazepine Acetate</i>	Eslicarbazepine acetate decreases mean plasma metformin C_{\max} values by 13 % and mean plasma metformin AUC values by 6 % [8].
<i>Lacosamide</i>	Lacosamide does not affect the pharmacokinetics of metformin [9].

Topiramate Topiramate decreases mean plasma metformin clearance values by 20 % and increases mean plasma metformin C_{\max} and AUC values by 18 and 25 %, respectively [5].

Metyrapone

Phenytoin Phenytoin enhances the metabolism of metyrapone and decreases metyrapone plasma levels [10].

Oxiracetam

Carbamazepine Carbamazepine decreases the plasma half-life of oxiracetam via an unknown mechanism [11].

Valproic Acid Valproic acid decreases the plasma half-life of oxiracetam via an unknown mechanism [11].

Pioglitazone

Topiramate Topiramate can decrease mean plasma pioglitazone AUC values by 18 % and can decrease mean plasma AUC values of its two pharmacologically active metabolites (a hydroxy-metabolite and a keto-metabolite) by 17 and 60 %, respectively [5]

Pizotifen

Topiramate Topiramate does not affect the pharmacokinetics of pizotifen [5].

Propofol

Valproic Acid Valproic acid reduces the dose of propofol required for sedation [12].

St John's Wort (*Hypericum perforatum*)

Carbamazepine Carbamazepine enhances the metabolism of pseudohypericin but not hypericin (the two main constituents of St John's wort), via an action on glucuronidation, and can decrease mean plasma pseudohypericin levels by 29 % [13].

Sumatriptan

Topiramate Topiramate can enhance mean plasma sumatriptan clearance by 11 % and decrease mean plasma sumatriptan levels by 10 % [3].

Theophylline

Carbamazepine Carbamazepine enhances the metabolism of theophylline and can decrease plasma theophylline half-life values by 48 % [14].

Phenobarbital Phenobarbital enhances the metabolism of theophylline and can increase mean plasma theophylline clearance values by 35 % and decrease mean plasma theophylline levels by 30 % [15].

Phenytoin Phenytoin enhances the metabolism of theophylline and can increase plasma theophylline clearance by up to 75 % [16, 17].

Tiagabine Tiagabine does not affect the pharmacokinetics of theophylline [18].

Tirilazad

Phenobarbital Phenobarbital enhances the metabolism of tirilazad, via an action on CYP3A4, and can decrease mean plasma tirilazad clearance by 25–29 % and can decrease mean plasma U-89678, a pharmacologically active metabolite, AUC values by 51–69 % [19].

Phenytoin Phenytoin enhances the metabolism of tirilazad, via an action on CYP3A4, and can increase mean plasma tirilazad clearance by 92 % and can decrease mean plasma U-89678, a pharmacologically active metabolite, AUC values by 93 % [20].

Tolbutamide

Clobazam Clobazam enhances the metabolism of tolbutamide and can decrease mean plasma tolbutamide AUC values by 11 % [2].

Triazolam

Rufinamide Rufinamide enhances the metabolism of triazolam and can decrease mean plasma triazolam C_{\max} values by 24 % and mean plasma triazolam AUC values by 36 % [21].

Valnoctamide

Carbamazepine Carbamazepine enhances the metabolism of valnoctamide and decreases valnoctamide plasma levels [22].

Zolpidem

Carbamazepine Carbamazepine enhances the metabolism of zolpidem and can decrease mean plasma zolpidem C_{\max} values by 39 % and mean plasma zolpidem AUC values by 57 % [23].

Valproic Acid Valproic acid does not affect the pharmacokinetics of zolpidem [24].

A pharmacodynamic interaction has been suggested between zolpidem and valproic acid whereby somnambulism occurs [24].

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- (2-chloroethyl)-1-nitrosourea (BCNU)

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